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Vol. 37 MARCH, 1955 No. 3

SURGERY

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SURGERY

VOL. 37 MARCH, 1955 NO. 3

Original Communications

THE IMPLANTATION OF CANCER—AN AVOIDABLE SURGICAL RISK?

LAUREN V. ACKERMAN, M.D., AND MYRON W. WHEAT, JR., M.D., ST. LOUIS, MO.

(From the Department of Surgical Pathology, Washington University School of Medicine, and Barnes Hospital)

LAWRIE,[1] in 1906, wrote a letter to the *British Medical Journal* and stated, "Where the original tumour has been removed entire inside a mass of surrounding tissue, like a core of paper in a ball of worsted, there will be no possibility of transplantation but when the tumour is broken into during an operation the risk of transplantation must be great. In such a case small portions conveyed by the fingers or knife might easily find a suitable position on the raw-surface for renewed growth, hence the so-called recurrence." This statement is still important today in the handling of neoplasms, and it is proposed to give some examples of transplantation of tumor during various types of operations, with various types of cancer under different circumstances. In most instances, implantation can be avoided by thinking of the possibility and by proper handling.

Needle biopsy is used as a diagnostic procedure in malignant tumors. Usually the skin is nicked, the needle inserted through the soft tissue into the neoplasm, suction is exerted, and a small fragment of tumor is removed, and then either smeared or sectioned. If the tumor has a capsule, then the needle will rupture the capsule, and the tumor could conceivably grow out through this needle tract, or small fragments of tumor will cling to the needle or drop from the needle and be deposited at some point along the tract. It is rare to find such complications reported and usually the information gained from needle biopsy far outweighs the risk. Johnson[2] has subserially sectioned lymph nodes removed after needle biopsy and identified the area in the capsule where the needle has entered. He has demonstrated that cancer will grow out through this tract and spread. Its growth is probably related somewhat to the local invasive properties of the neoplasm. In the case illustrated, a squamous carcinoma grew out for a short distance along the tract in sixteen days (Figs. 1 and 2). In another instance, malignant melanoma grew out along the tract, up almost to the skin surface, after nine days.

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If needle biopsy is to be performed on lymph nodes, then this possibility must be considered when surgery is later embarked upon. We would be against needle biopsy in situations where incisional biopsy is much more prac-

Fig. 1.

Fig. 2.

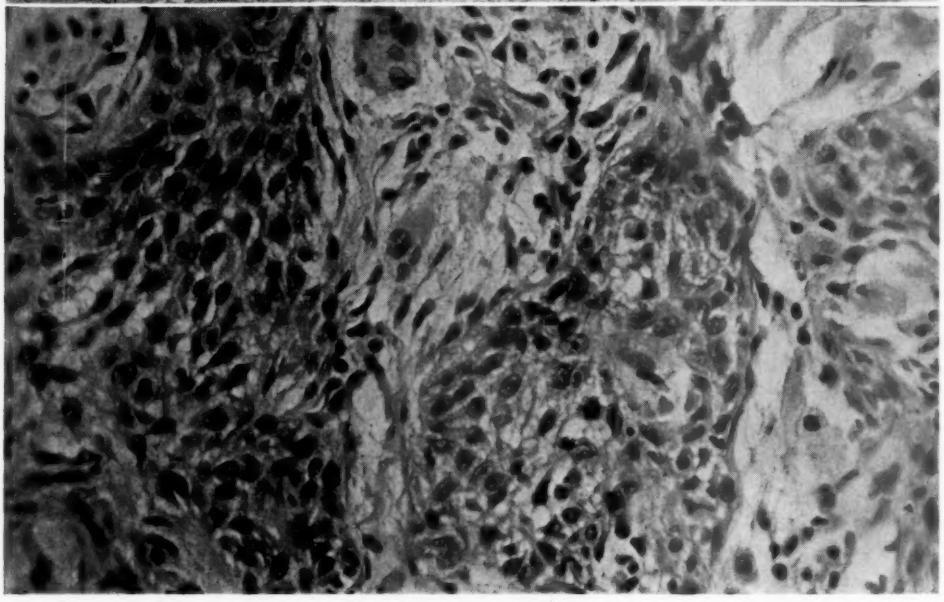


Fig. 1.—Photomicrograph of excised skin and portion of a node. The needle points to the tract made sixteen days previously. (W.U. #54-1153A.)

Fig. 2.—This represents undifferentiated squamous carcinoma in the needle tract, demonstrated in Fig. 1. (W.U. #54-1154A.)

tical, as in the breast, and we see no point in performing needle biopsy in debatable lung lesions. The possibility exists, with needle biopsy of renal tumors, that the tumor can grow back along the tract, and in cancer of the prostate such implantation has already occurred at the site of a perineal needle biopsy.[3]

Skin grafting: In skin grafting for malignant tumors, if the instruments, gloves, and drapes are not changed and the operator uses the instruments he has been using in the region of the cancer, it is possible to transfer cancer to the region of the skin graft. This has already been reported by Brandes[4] in cancer of the breast. In this patient, after mastectomy and before the skin grafting, the operator's and assistant's gloves were washed in distilled water but were not changed. Centrifuging the fluid demonstrated well-preserved tumor cells. We have seen transplantation of tumor to the skin graft area at the time of excision of a squamous carcinoma of the skin, and this has been reported also by Hubbard.[5] Saphir[6] has identified viable tumor cells on knives used in surgical biopsy or excision. We have seen a patient (male, aged 75) with a plasma cell tumor of the chest wall. This tumor was excised in March, 1948; it was necessary to graft the chest area, and the operator implanted tumor on the graft site of the leg. This was apparent three months later. This was later treated successfully by irradiation therapy. To avoid this risk, it is necessary, therefore, to change not only instruments but also gloves and drapes.

Implantation during head and neck surgery: In operations on the parotid salivary gland, inexperienced surgeons frequently enucleate a mixed tumor and, in so doing, rupture the capsule of the tumor and implant nodules widely into the surrounding tissue. This leads inevitably to clinically apparent, persistent tumor, and it is often difficult to excise the seeded zones adequately. We have subserially sectioned tissue removed at the time of operation for a persistent mixed tumor of the salivary gland in which the first operation had been an inadequate enucleation. Fig. 3 demonstrates the wide distribution of the implantation at the time of the first surgical procedure. We have also seen mixed tumor implanted in the skin of the neck. It used to be considered that, if a patient had a highly functioning tumor of the parathyroid, at times it might be wise to remove just a portion of the neoplasm. This is no longer thought necessary. In one of our cases of a *parathyroid* cancer, it was inadequately removed and implanted in the soft tissue, where it grew, recurred, invaded, and finally caused the death of the patient (Case 20, No. 57812[7]). Benign parathyroid adenoma can also be transplanted, and this was done deliberately by Burke.[8] This resulted in a regrowth of the lesion with recrudescence of function.

The same principle applies to the *thyroid* gland, where often there is a single, dominant nodule. This dominant nodule may be a benign tumor, a malignant tumor, or an expression of a nodular goiter. If it is a malignant neoplasm and is enucleated or even biopsied, then it may be implanted in the neck, and the recurrence of such lesions is difficult if not impossible to handle. Frantz[9] has reported two instances of local recurrent papillary carcinoma of

the thyroid following an incisional biopsy. We have seen a woman, aged 43,[7] with a tumor of the *thyroid* which was thought to be benign, which was enucleated in 1947 (No. 57410). A subcutaneous nodule appeared seven years later in 1954 (No. 54-2258) and was found to be persistent carcinoma (Fig. 4). We believe a single nodule should be treated by excision of the lobe and at least by a margin of normal thyroid.

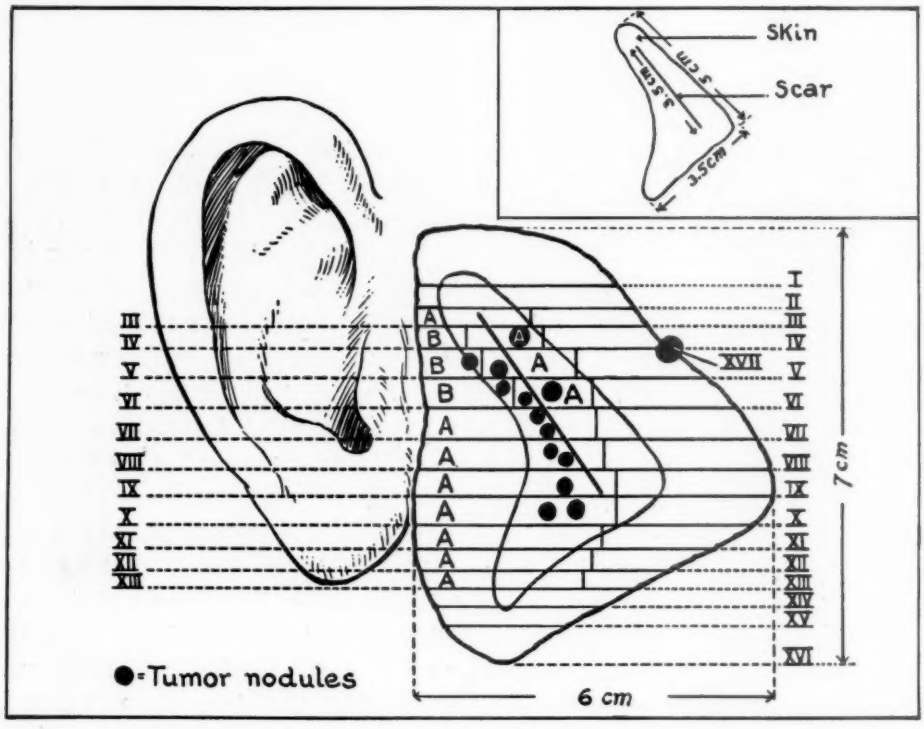


Fig. 3.—Schematic representation of nodules of tumor found in a persistent mixed tumor which had been previously enucleated. Note the wide extent of this neoplasm. (From Ackerman, L. V.: Surgical Pathology, The C. V. Mosby Company.)

Surgery of soft tissue and bone; exclusive of mediastinum and retroperitoneal area: We have recently reviewed 100 consecutive cases of soft-tissue sarcomas. Unfortunately, these neoplasms were often first treated by primary surgery without the benefit of biopsy. These sarcomas clinically and at exploration appear to be encapsulated and for that reason are often enucleated, with the result that tumor is implanted over a wide area. This may convert a relatively fortunate clinical situation to one in which cure, even by the most radical surgery, is impossible. For instance, this sequence of events can occur when the tumor is located in the deep soft tissue of the upper, inner surface of the thigh. Enucleation of the tumor in this area may cause implantation of sarcoma over the entire zone, forcing amputation or even hemipelvectomy. A review of our cases demonstrated the importance of preliminary biopsy and then properly planned surgery, in contrast to those in which no biopsy was performed.[10] Fig. 5 demonstrates the difference in the instance of local persistence in these two groups.

By contrast, proper handling of a large soft-tissue tumor is exemplified by a patient (aged 53) who had an 8 by 6 cm. tumor involving the soft tissues of the chest. Radiographs demonstrated involvement of the rib cage; a preliminary biopsy indicated that it was an undifferentiated liposarcoma. The tumor with adjoining ribs and underlying pleura was resected. This patient is now living almost five years without evidence of disease (Fig. 6). Therefore, in the treatment of a soft-tissue tumor, careful incisional biopsy should first be performed, followed by adequate surgery including the zone through which biopsy was performed.

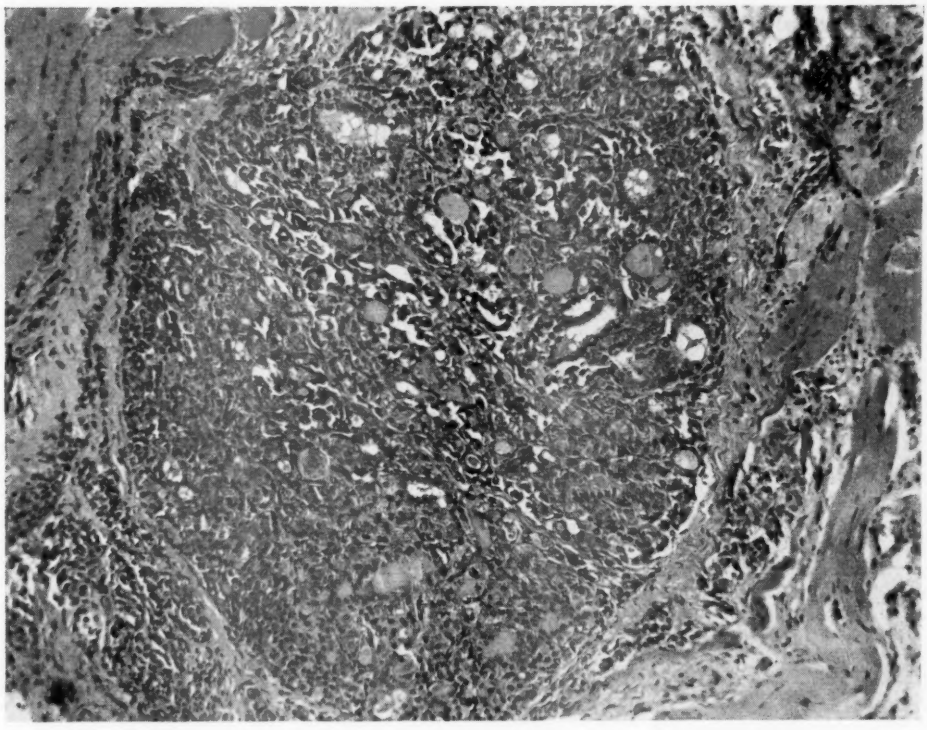


Fig. 4.—Well-differentiated thyroid cancer implant in the skin of the neck seven years after the removal of the primary tumor. (W.U. #54-2862.)

In the treatment of neoplasms of bone, it is imperative that a definitive diagnosis be available before adequate surgery is carried out. It is unfortunate that many of the patients with malignant bone tumors are young, and frequently they are not cured even by the most carefully planned procedures. The interpretation of bone sections is often difficult, and it is obviously impossible to be sure of the diagnosis by radiographs alone. Careful incisional biopsy of most bone tumors, particularly those peripherally situated, such as at the lower end of the femur or the upper end of the tibia, will not prejudice adequate surgery, and even if tumor is locally implanted during biopsy, it will obviously be excised by the amputation. There are certain locations that are fraught with danger from the standpoint of implantation. An area that is particularly dangerous is the upper end of the femur. If the incisional

biopsy is not carefully planned, implantation into the soft tissue inevitably occurs, and disarticulation will not then be an adequate procedure and even hemipelvectomy will be prejudiced. A good example of this is represented by the patient who had an osteolytic defect in the upper end of the femur (Fig. 7). This was biopsied (Fig. 8) and proved to be a well-differentiated chondrosarcoma. A disarticulation was performed (Fig. 9), but the patient unfortunately developed pulmonary metastases (Fig. 10) and died. At the time of post-mortem examination, there was locally persistent tumor at the site of the disarticulation. At the time of exploration for biopsy, there had been no perforation of the cortex. The operator was not sure of the diagnosis, the lesion was hemorrhagic, and he obviously seeded the soft tissues widely. Another difficult zone is in the pelvic bones. In this zone and in other areas where there is a possibility that a malignant bone tumor exists, the planning for biopsy must be very careful in order that if amputation is necessary, then it will encompass the zone of biopsy.

Joynt[11] reported a patient with a giant-cell tumor of the upper end of the tibia. This lesion was curetted and the defect replaced by a sliding bone graft from the tibia, and the remainder of the cavity was packed with cancellous bone chips from both iliac crests. The cancellous bone graft was removed *after* the curettement of the tumor. A mass appeared one year later beneath the skin and attached to scar tissue overlying the ilium. This was excised, and the tumor had all the characteristics of the giant-cell tumor of bone. This case demonstrates the possibility of transplantation of microscopically benign giant-cell tumor during bone grafting.

FIG. 5.—CLINICAL EVALUATION OF PRELIMINARY BIOPSY

	NO. OF CASES	LOCAL RECURRENCES
Without biopsy	27	21 (78.8%)
With biopsy	12	2 (16.6%)
Total	39	23 (59.9%)

Lungs and bronchus: In the surgery of lung tumors, the diagnosis before surgery is made on biopsy in only about 30 per cent of instances. Cytology will make the diagnosis in another 40 to 50 per cent. Therefore, there remain 20 to 35 per cent of patients in whom a definitive histological examination is not available. In the *bronchus* we have seen an instance in which a surgeon used a cautery in biopsying a so-called bronchial adenoma. This tumor was later resected by surgery, but it was obvious from study of the sections that the operator had transferred cells to the proximal bronchus at the time of cautery biopsy and the surgeon had transected tumor at that point, suggesting that future local regrowth of tumor is almost certain. At the time of exploration for a suspected malignant lung tumor in which positive cytologic findings or bronchoscopic biopsy is not available, frozen section is often resorted to. In the small, peripherally located round lesions, we suggest that local resection be carried out or, if this is not feasible because of size, that consideration of lobectomy be entertained. We have now seen two

instances in which a peripheral lung tumor was broken into at the time of surgery. Both of these tumors were relatively low-grade carcinomas and both locally recurred and grew out through the chest wall. Certainly, care must be taken in doing frozen sections, and in our hospital, when such a biopsy is necessary, the zone is packed off, a careful incision is made, the zone is closed, the packs are discarded, and gloves and instruments are changed.

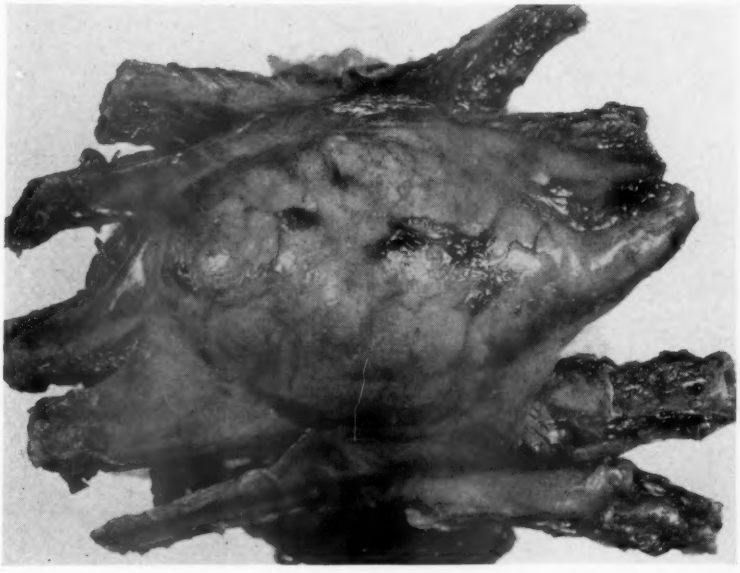


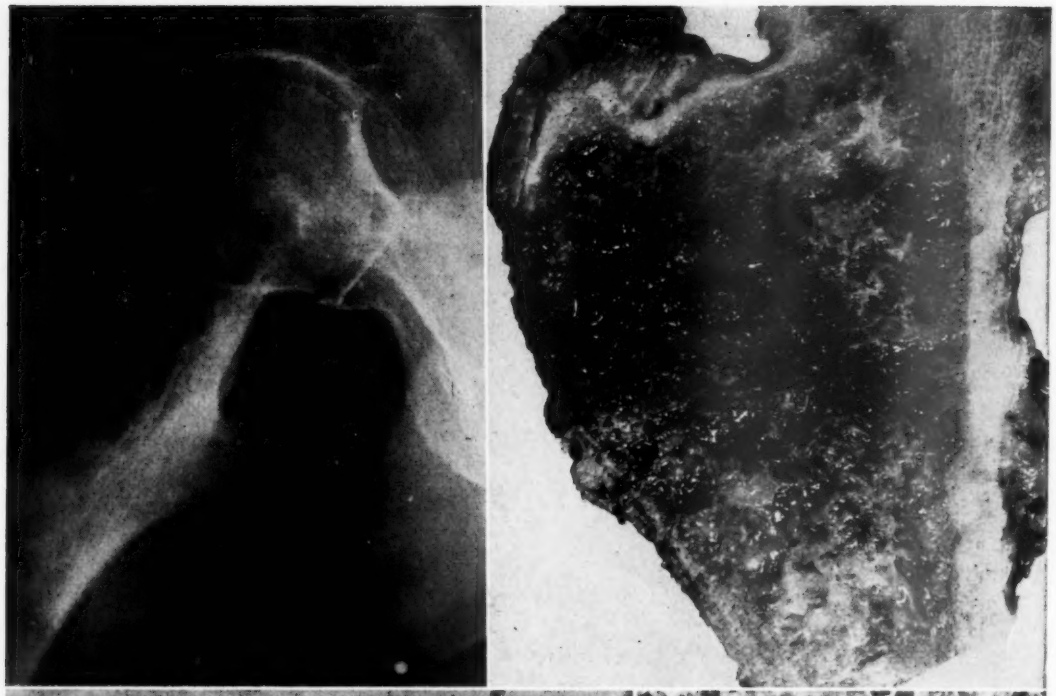
Fig. 6.—Gross photograph of a large soft-tissue liposarcoma of the chest wall which was resected with adjoining ribs and underlying pleura. This patient has remained well for over five years. (W.U. #49-1800.)

Pancreas and periampullary area: The clinical diagnosis of carcinoma of the pancreas and other carcinomas from the periampullary area is extremely difficult before operation. At the time of surgery, it is also often difficult to be sure that one is dealing with a carcinoma in that zone. The operative mortality as well as morbidity is extremely high for one-stage pancreatoduodenectomies. It is also unfortunate that the cure rate for carcinomas of the head of the pancreas is practically zero. In lesions involving the ampulla, rarely it may be possible to obtain a positive cytologic diagnosis before operation and thus avoid biopsy at operation.[12] We have felt that it is imperative to have a positive diagnosis before embarking upon this formidable surgical procedure. We have felt that the danger of implantation is always present and that every effort must be used to avoid this complication. The following history demonstrates how implantation can occur, and it was particularly unfortunate because this patient, on the basis of the pathologic findings, would have appeared to have had an excellent prognosis.

The patient, a man aged 60, had a biopsy with frozen section of carcinoma of the ampulla. It proved to be a very well-differentiated adenocarcinoma. Resection was performed easily, and careful pathologic studies showed no evidence of nerve sheath invasion, no lymph node metastases, and the only tumor present was in the frozen section. The pa-

Fig. 7.

Fig. 9.



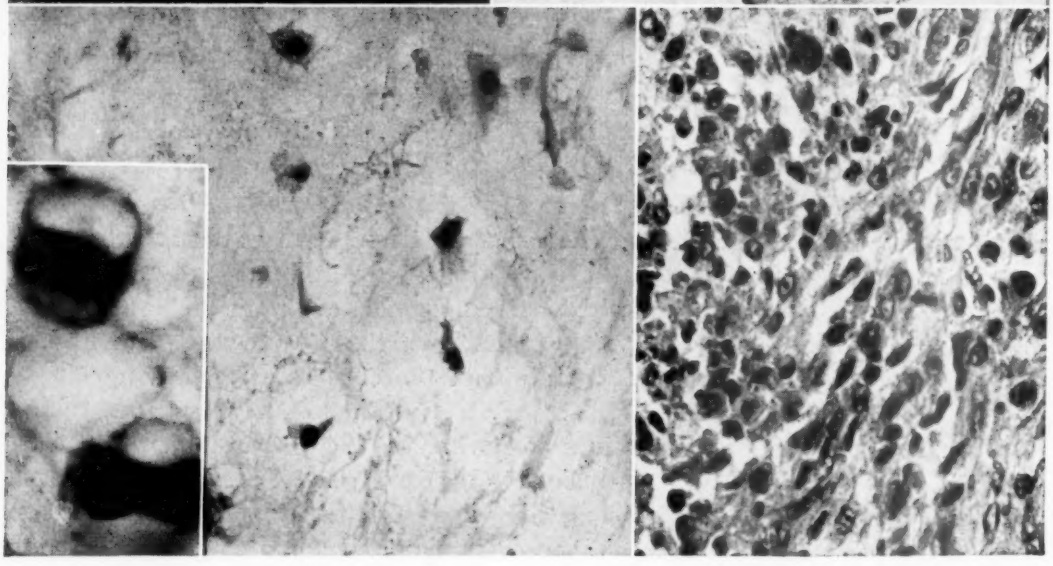


Fig. 8.

Fig. 10.

Fig. 7.—Osteolytic defect in the upper end of the femur due to chondrosarcoma. (W.U. #49-4395.) (From Ackerman, L. V.: Surgical Pathology, The C. V. Mosby Company.)

Fig. 8.—Scattered malignant cartilage cells with prominent nuclei and double nuclei. (W.U. #50-2301A.) (From Ackerman, L. V.: Surgical Pathology, The C. V. Mosby Company.)

Fig. 9.—Gross photograph of resected chondrosarcoma. Note disruption of the cortex in upper left portion of the specimen which was the area of biopsy. (W.U. #49-4323.) (From Ackerman, L. V.: Surgical Pathology, The C. V. Mosby Company.)

Fig. 10.—Undifferentiated chondrosarcoma growing in the lung at the time of post-mortem examination. (W.U. #50-2302.) (From Ackerman, L. V.: Surgical Pathology, The C. V. Mosby Company.)

tient developed a ventral hernia and this was repaired two and one-half years after the resection. At that time the abdomen was explored and a small nodule of persistent tumor was found in the region of the ligament of Treitz. This was similar to the primary tumor. We can only infer that it was implanted at the time of the first operation (Fig. 11).

Surgery of the large bowel, small bowel, and stomach: It has now been demonstrated by Golighter,[13] Cole,[14] and at Barnes Hospital, St. Louis, that

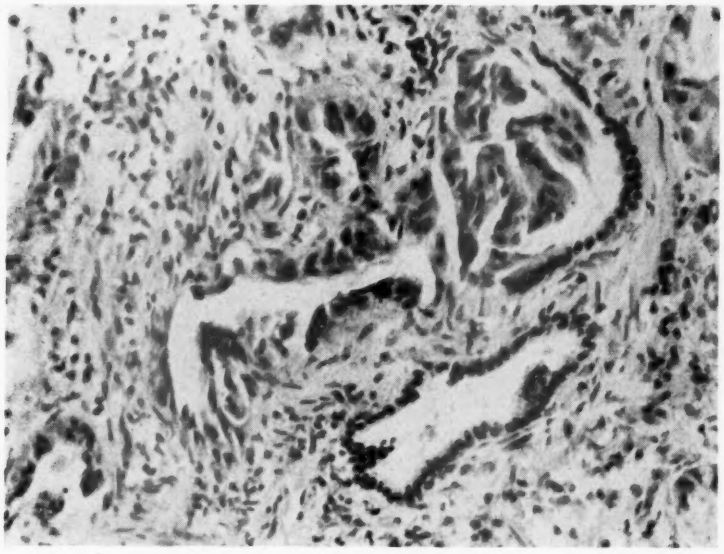


Fig. 11.—Well-differentiated adenocarcinoma of the ampulla, persistent in the peritoneal cavity. (W.U. #54-1152.)

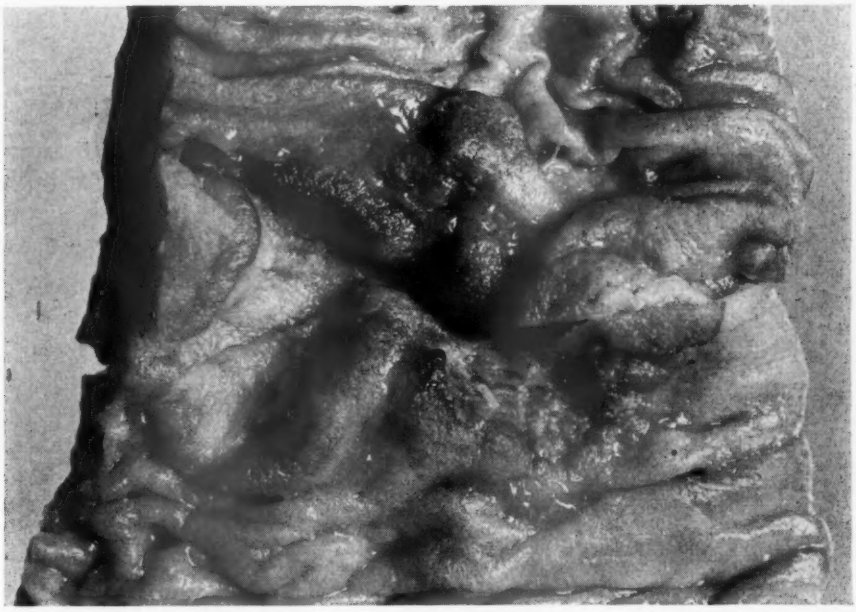


Fig. 12.—Gross photograph of persistent adenocarcinoma of the large bowel. (W.U. #52-3319.)

implantation of carcinoma at the suture line can occur during the course of operations for carcinoma of the large bowel. It has been demonstrated that carcinoma cells are free within the lumen of the bowel,[15] and it has been shown

Fig. 13.

Fig. 14.

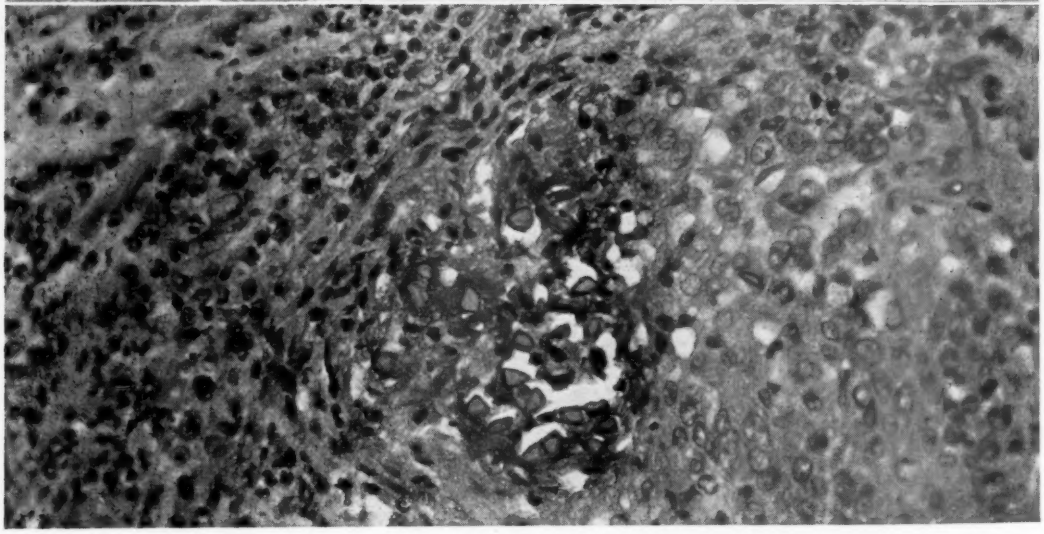


Fig. 13.—Photomicrograph of the adenocarcinoma growing within the wall of the bowel, but confined to it. Arrow points to suture material. (W.U. #52-5864A.)

Fig. 14.—Photomicrograph of the suture material within the wall. (W.U. #52-5865A.)

by Golighter[13] that tumor apparently grows rather easily on the raw surface of the bowel at the point of the suture line. The following case is a classical example of such an implantation:

The patient, a man aged 75, had a resection of the sigmoid colon on Nov. 10, 1950. At a point 1.5 cm. from the distal end and 5 cm. from the proximal end, there was a 4.4 by 3.5 cm. ulcerative tumor mass. One of twelve lymph nodes was involved. There was involvement of the muscular wall but no extension through it. On May 6, 1952, eighteen months later, the patient developed local recurrence, and abdominal perineal resection was performed. Regional lymph nodes were not involved. The gross specimen demonstrated a tumor which was confined to the wall, without lymph node involvement, and microscopically this tumor was growing in the region of the suture line and remnants of suture material could be identified[13, 14] (Figs. 12, 13, and 14).

Fig. 15.—Gross photograph of large papillary adenocarcinoma of the rectosigmoid area. Confined to mucosa and submucosa without lymph node involvement. (W.U. #54-2967.) Specimen contributed by Dr. Robert Bartlett, St. Louis, Mo.

We also feel that local recurrence in carcinoma of the rectum following abdominal-perineal resection is often due to cutting through tumor and carrying it into the regional soft tissues. We have frequently seen such local recurrence appear directly beneath the incision in the region of the anus. These findings also emphasize the dangers of conservative resections of carcinomas of the rectum, and the importance of the lateral extent of the tumor. Mayo[16] reported implantation of a cancer into a left rectus colostomy wound. A two-stage operation for carcinoma of the rectum was performed with a double-barreled colostomy. At the second stage, the sigmoid was divided six inches above the growth, and the end was turned in and left as a blind attachment. Seven weeks later the patient returned with a carcinomatous growth in the inner edge of the colostomy opening. This was excised, and he has been all right. We have had a patient, a 60-year-old man, with carcinoma of the stomach which was explored in September, 1948. The surgeon opened the stomach, biopsied the lesion, and did nothing further. The patient was re-explored two months later and the lesion was found to be resectable. There was no evidence of lymph node involvement, and the tumor penetrated the wall of the stomach but did not involve the serosa. One year later the patient re-

entered the hospital with a mass in the transverse scar of the first operation. This mass was resected and found to be adenocarcinoma. It was apparently implanted at the time of the first surgical procedure. The patient remains well today, approximately five years after the first procedure. This case demonstrates that it is at times possible to resect implanted neoplasm with possibility of cure.* It is also possible to implant tumors of the gastrointestinal tract into

Fig. 16.

Fig. 17.

Fig. 16.—Gross photograph of implantation of this tumor within the abdominal wall, apparent three years after original resection of tumor depicted in Fig. 15. (W.U. #54-2966.)

Fig. 17.—Photomicrograph of the tumor growing within the abdominal wall. Note its excellent differentiation. (W. U. #54-2864A.)

*Case contributed by Dr. Heinz Haffner, St. Louis.

abdominal wall in the area of the incision. We had a patient with a large papillary adenoma of the rectosigmoid region; we had operated in 1949; a subcutaneous implant became apparent in 1952 and was resected (Figs. 15, 16, and 17).

We would also feel that this chance of local implantation into the suture line or into other more distant zones must occur in the treatment of malignant tumors of the esophagus, stomach, and small bowel. It is probable that some of the local recurrences of carcinomas of the stomach are not due to primary inadequate excision, but are in reality due to implantation along the suture line.

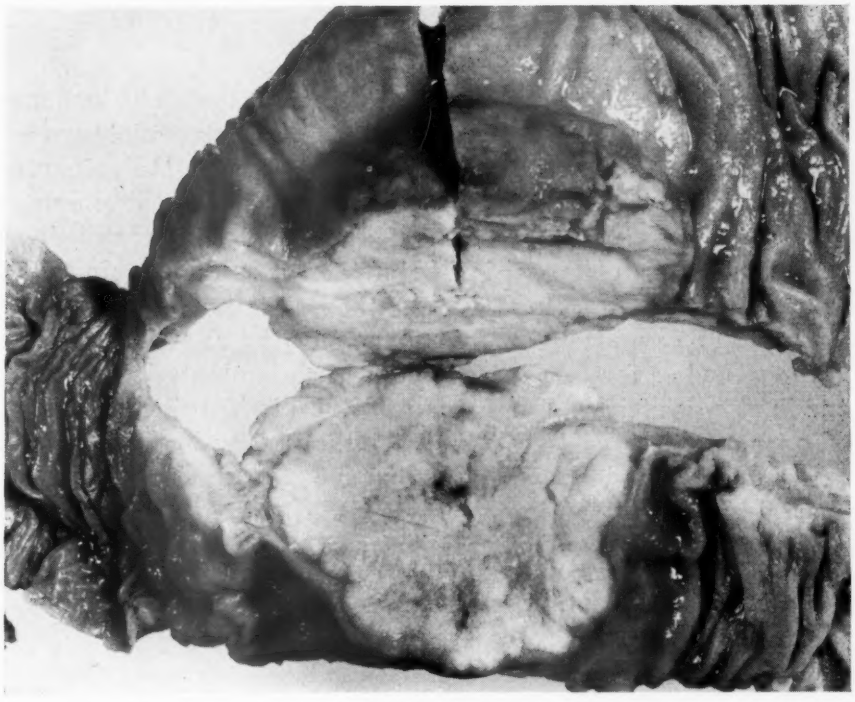


Fig. 18.—Gross photograph of carcinoma of the endometrium implanted in the wall of the rectosigmoid and resected eighteen months after the primary operation on the uterus. Note tumor growing beneath intact mucosa. (W.U. #54-3146.)

Operations on ovaries and uterus: In operating on ovarian cancers, of course, rupture can occur with implantation on the peritoneal surface. It is not as well known that implantation into the abdominal wall can also take place. Dvorak[17] reported such an instance with a local recurrence within the abdominal wall thirteen years after operation on an ovarian neoplasm. In operations on the *uterus* for carcinoma of the endometrium, if the operator ruptures the uterus, local implantation can occur. Carcinoma of the endometrium is usually a slowly growing, easily cured carcinoma. We have had a patient, a 70-year-old woman. At the time of hysterectomy in September, 1952, the operator tore the uterus with his tenaculum. Eighteen months later the patient developed an extramucosal mass in the rectosigmoid area (Fig.

18). Abdominal perineal resection was performed, revealing a well-defined tumor nodule in the wall. Regional nodes revealed no evidence of tumor, and the microscopic sections of both tumors were identical.

Implantation of *renal* parenchymal carcinoma has already been reported by Hovenanian[18] into the ureteral stump, possibly due to the manipulation during surgery. If tumor is torn into during the time of the operative procedure, it will certainly be implanted in the surrounding areas. Better approaches to renal cell cancer, such as the thoracolumbar approach, will do much in reducing implantation.[19] *Bladder* cancer can also be implanted into the abdominal wall. Mayberry[20] reported such a case, and Lumb[21] also reported another and stated that the cancer was present along with suture material.

CONCLUSIONS

The main purpose of this discussion is to cite instances of implantation at the time of biopsy or definitive surgery. Implantation is not always avoidable. However, the risk is frequently not considered, and often the precautions that are available are not taken. Furthermore, the tumor that again appears after surgery may be the result of poorly planned surgery rather than being present beyond the zone of possible excision. However, it seems certain that in some instances the surgeons are not considering the risk of implantation. Certainly, implantation can be avoided in many instances by the changing of instruments, gloves, drapes, and so forth. If this is done, such implantation certainly could not occur in skin grafting. Furthermore, if needle biopsies are well planned, the needle tract will be excised along with the involved organ, and regrowth of tumor cannot take place. In other instances, the primary tumor may be removed, and tumor will be implanted at a distance, will later become clinically apparent, and be excised with possibility of cure.

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PRIMARY CANCER OF THE LIVER

An Eight-Year Survey of New Orleans, Louisiana

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THE difficulty inherent in the diagnosis of primary carcinoma of the liver has been brought to our attention by two cases which we studied for prolonged periods. If earlier diagnosis or suspicion were possible, one could save some of the unnecessary expenses of prolonged hospitalization and multiple laboratory tests. To justifiy the increasing interest in resection of the liver, earlier diagnosis must be made so that a surgical attack on this disease might be feasible.

The patient who originally stimulated our interest in this subject is typical of the prolonged hospitalization (in this case two months prior to surgery), the extensive work-up, and the failure to think of the proper diagnosis, all so frequently seen in this condition. The importance of an early, aggressive attitude in preventing repetition of this unnecessary delay is apparent.

J. B., a 42-year-old Negro woman, was admitted with pain in the abdomen and chest, cough, fever, chills. During the preceding six months she had lost 30 pounds. There was no history of jaundice or edema. Physical examination revealed questionable liver tenderness, jaundice, nonpalpable liver. Multiple blood counts revealed a slight anemia, white count ranging from 9,500 to 12,650, with segmented forms ranging from 65 per cent to 92 per cent. Routine urinalyses failed to reveal anything of note. Stools were negative for ova, parasites, and cysts on at least seven different occasions. Serology was negative. All available agglutinations were negative on two different occasions. Cephalin flocculations were made six times, with values ranging from negative through 3 plus. Icterus index, determined four times, ranged from 11.9 through 67. Five bilirubin determinations ranged from 0.3 to 1.9. Thymol turbidity was done six times, with a range from 1.5 through 11. Sputa were examined for acid-fast bacilli on seven occasions, with uniformly negative results. Three blood cultures were negative. Chest x-ray films were taken six times, showing elevation of the leaves of the diaphragm. Three attempts at cholecystography were negative. Two flat plates of the upper abdomen gave evidence of an ill-defined density. Gastrointestinal series were done twice, showing only gastric retention. Barium enema was normal.

The patient was given several courses of antiamebic therapy on the basis of a suspected diagnosis, which could never be confirmed. She was finally submitted to surgery, even then with a working diagnosis of a subsiding acute, or possibly an old perforated and walled off, gall bladder. It was only when the abdomen was opened and the liver was found to be studded with innumerable small malignant deposits that the diagnosis became obvious. She did well for a short time after surgery, but expired about three weeks after operation.

In the hope that a careful re-evaluation of the cases might serve to bring out some points in the clinical history, physical findings, laboratory studies, or

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population incidence that might make one more alert to primary cancer of the liver in the future, a survey of its incidence in the city of New Orleans was undertaken. Only those cases proved by histologic section from January, 1945, through December, 1952, are included, a previous survey of two of the hospitals included in our study having been made from 1937 to 1944.[1] Inclusion of all major hospitals whose patient load is predominantly from New Orleans gives an estimate of the incidence of this condition in one American city of approximately one-half million population. We are aware of two difficulties: (1) Since many of the patients in Charity Hospital come from various parts of the state, the incidence of the disease might be artificially raised. However, this is compensated by discarding many patients whose diagnosis seems well established on all but histologic grounds. (2) Patients not admitted to a hospital are not included. Since the majority of patients with primary carcinoma of the liver are hospitalized prior to the terminal episode, this error would also tend to be minimized.

TABLE I. INCIDENCE AND METHOD OF DIAGNOSIS

HOSPITAL	CHARITY	SARAH MAYO	FLINT GOODRIDGE	TOURO	HOTEL DIEU	BAPTIST	TOTAL
Total admissions	472,170	21,612	20,912	134,655	95,989	139,432	884,770
Diagnosis							
Clinical	11	0	0	0	1	0	12
Surgery	11	0	1	0	4	4	20
Autopsy	15	0	0	5	0	4	24
Total	37	0	1	5	5	8	56
Admissions per diagnosis	12,761	0	20,912	26,931	19,198	17,429	15,799

A total of fifty-six cases have been found between 1945 and 1952. During this time 884,770 patients were admitted to the six hospitals studied, making an over-all incidence of one proved diagnosis of primary cancer of the liver in 15,799 admissions. The rate of diagnosis varies from that of Charity Hospital, with one diagnosis per 12,761 admissions, to that at Touro Infirmary, with one diagnosis per 26,931 admissions. Charity Hospital, with the highest incidence of diagnoses, also had the greatest number and greatest per cent of clinical diagnoses. Conversely, the hospital with the lowest incidence is the only one where all cases were diagnosed at autopsy.

TABLE II. HISTOLOGIC DIAGNOSIS

Primary liver cell-type carcinoma	50
Cholangiocarcinoma	5
Sarcoma	1
Total	56

The incidence of this disease has increased in this area. In a previous report, an average of 2.9 cases a year were found at Charity Hospital from 1928 through 1944.[1] During the eight years currently under study, thirty-seven cases were found in the same institution, to give a yearly incidence of 4.5.

The disease is approximately five times as common in the male as in the female. The greater incidence in the Negro female than in the white and the occurrence at both earlier and later ages in males may both be due to chance since there were so few females in the entire series. The apparently higher incidence in white patients was not confirmed at Charity Hospital, where 65 per cent of total hospital admissions were Negroes and 67 per cent of the patients were Negroes (twenty-five Negro and twelve white patients).

TABLE III. AGE, SEX, AND RACE DISTRIBUTION

		AGE (YR.)								
	TOTAL	0-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75 AND OVER
White male	26	4	0	4	1	3	4	7	2	1
Negro male	22	4	2	1	4	1	3	2	4*	1
White female	3	0	0	1	1	0	1	0	0	0
Negro female	5	0	1	1	1	0	2	0	0	0
Total	56	8	3	7	7	4	10	9	6	2

*Includes one Chinese.

TABLE IV. CHIEF COMPLAINTS

Abdominal pain		41
Pain in stomach	16	
Epigastric pain	10	
Right upper quadrant pain	5	
Right side pain	4	
Umbilical pain	3	
Lower abdominal pain	1	
Left upper quadrant pain	1	
Gas pain	1	
Gastrointestinal dysfunction		16
Nausea	4	
Vomiting	4	
Hematemesis	2	
Melena	1	
Poor appetite	1	
Weight loss	1	
Weakness	1	
Loose bowels	1	
Stomach trouble	1	
Abdominal enlargement		10
Abdominal distention	7	
Fullness	1	
Bloody ascites	1	
Water on stomach	1	
Chest pain		7
Pain in chest	2	
Right chest	2	
Left chest	2	
Right costal margin	1	
Mass		8
Right upper quadrant mass	3	
Mass in stomach	2	
Epigastric mass	2	
Mass upper abdomen	1	
Miscellaneous		17
Jaundice	3	
Cough	3	
Fever	2	
Each of following:	1	
Swollen liver, shortness of breath, dyspnea, swollen legs, shoulder pain, coma, convulsion, generalized pruritis		

History.—A careful history and physical examination are of the utmost importance, since study of the present series would indicate that there is no clear-cut, classical clinical picture which would identify the condition at first glance. An early suspicion of the disease, based on the pertinent findings in history and physical examination, is essential if the diagnosis is to be established at an early stage when some therapy might be valuable. Any symptoms which might suggest this disease should be emphasized, since our fifty-six patients had ninety-six chief complaints.

The four commonest chief complaints, any one of which should immediately raise suspicion of primary cancer of the liver, were:

1. Unexplained pain in the abdomen.
2. Vague gastrointestinal dysfunction.
3. Otherwise unexplained abdominal distention or an abdominal mass.
4. Unexplained chest pain.

TABLE V

	NUMBER QUESTIONED	PER CENT POSITIVE
History		
Urine color change	23	95.8
Weight loss	47	87.2
Visible or palpable mass	16	81.2
Edema	26	65.4
Stool color change	34	55.9
Nausea or vomiting	47	51.1
Previous diagnosis of cirrhosis	6	50
Alcoholic history	23	43.5
Jaundice	30	36.8
Sweats	15	20
Chills	17	15
Physical Examination		
Liver palpable	50	90
Jaundice	39	66.6
Evidence of weight loss	39	66.6
Liver tenderness	42	54.8
Evidence of portal obstruction	23	52.2

Weight loss, particularly if combined with any of the complaints mentioned previously, should be considered suspicious of cancer of the liver. There was a history of weight loss in 87.2 per cent of the patients, ranging from 6 to 100 pounds, and averaging 30.7 pounds. In two-thirds of the patients there was evidence of weight loss on physical examination.

A change in the color of the urine was reported by 95 per cent of the patients, and should be a further aid in establishing this diagnosis.

A visible or palpable mass detected by the patient is an extremely important feature in leading to the diagnosis, since the liver was palpable in 90 per cent of this series. In one-half of these patients it was smooth and in one-half it was nodular, so that the character of the liver edge could not be diagnostic in itself. Liver tenderness and evidences of portal obstruction, found in slightly over one-half the patients, should be of some diagnostic assistance.

Abdominal pain was the chief complaint of forty-one patients and therefore the most frequent chief complaint in the study. As can be seen in Table VI, pain was variously localized to all parts of the abdomen, and even to the chest. Pain specifically located on the left side only occurred once, thus further emphasizing the importance of symptoms in the general area of the liver itself. Three-eighths of the patients reported a sharp, severe pain, and two-eighths classified the pain as cramping or burning. A similar number noted only a dull, inconstant pain, or simply tenderness. The character of the pain is thus seen to be as variable as was its location, both of which will significantly add to diagnostic difficulty, unless the diagnostic possibility of carcinoma of the liver is kept in mind.

TABLE VI

Pain Characteristics	
Knifelike, sharp, severe	16
Aching, cramping, stinging, gnawing, burning	10
Dull, gaslike, inconstant, postprandial, tenderness	12
Constant	2
Pain Location	
Epigastrium	20
Right upper quadrant	8
Right chest	4
Abdomen	3
Right lower quadrant	3
Right side	2
Lower abdomen	2
Right costovertebral angle	1
Infrascapular region	1
Left upper quadrant	1
Upper abdomen	1

Peripheral edema, change in the stool color, and nausea and vomiting each occurred in over 50 per cent of the patients, and therefore should be noted with care.

Primary cancer of the liver is usually thought to be associated with cirrhosis. The surprisingly low incidence of only three patients in this series who had a previous diagnosis of cirrhosis is thus worthy of comment. The over-all incidence of cirrhosis was likewise unusually low, and will be considered in detail later. Less than one-half the patients had an alcoholic history, and this cannot be considered of major importance in the present series. Jaundice, an important factor in any condition where liver disease is suspected, was noted in approximately two-thirds of these patients.

Temperature elevation has frequently been considered characteristic of primary cancer of the liver. In the nine patients where this could be evaluated during a minimal two-week hospitalization prior to any operative procedure, four had almost daily spikes ranging from 99 to 103, while five had normal temperatures. Thus temperature elevation was not a constant finding.

The duration of complaints ranged from two days to four years, with seven patients having symptoms more than one year. The median duration of symptoms was two months.

Laboratory Examinations.—Seven laboratory examinations were positive in over 70 per cent of the cases. An elevated van den Bergh test was the only consistently positive finding, and varied from 0.7 to 39.5. Icterus index varied from 5 to 227. Thymol turbidity was more frequently positive than the cephalin flocculation, even though the latter was used more commonly. Elevation of cholesterol and alkaline phosphatase, and albumin-globulin ratio abnormality complete the studies that were positive in more than 70 per cent of the patients.

TABLE VII. LABORATORY EXAMINATIONS

	NUMBER EXAMINED	PER CENT POSITIVE
Van den Bergh test	18	100
Icterus index	36	88.8
Alkaline phosphatase	7	85.7
Thymol turbidity	26	84.6
Albumin globulin ratio	15	80
Cephalin flocculation	36	72.2
Cholesterol	7	71.4
Bromsulphalein	13	61.6
Prothrombin time (original)	17	58.8
Prothrombin time (subsequent)		41.2
Urinalyses	49	22.5
Serum protein	36	22.2
Stool	23	21.7
Serologic test for syphilis	42	14.3
Bleeding time	11	0
Coagulation time	10	0

An elevated prothrombin time returned to normal during the hospitalization of some patients so that eventually it was positive in only 41.2 per cent. Whether this was due to vitamin K therapy, transfusions, nutritional changes, or something else, we cannot say. Bromsulphalein retention gave positive results in 61.8 per cent, with five of the eight abnormal values being above 25 per cent.

Total proteins were infrequently abnormal, but albumin-globulin ratios were above 2.5 in two and below 1.5 in ten, so that some importance could be attached to this ratio.

Bleeding and coagulation times, urinalyses, stool examinations, and serologic tests for syphilis were so infrequently positive as to be of little diagnostic aid.

Red blood counts, hemoglobin, and white cell counts were almost routinely in the normal range.

X-Ray Studies.—Gastrointestinal x-ray studies should be used extensively in such perplexing clinical problems. Fourteen patients had both upper gastrointestinal series and a barium enema, and eleven patients had cholecystograms. Even though these studies may not give a diagnosis, entirely negative results may help to point to a diagnosis by exclusion.

Of the eleven patients who had gall bladder studies, eight failed to visualize, two were reported as normal, and one was reported simply as "negative." In view of the extensive hepatic damage often present, nonvisualization in eight cases is not surprising.

On upper gastrointestinal studies (thirty-one cases), eleven had evidence of extrinsic pressure on either stomach, duodenum, or both, and one was interpreted as having an intrinsic gastric lesion. Negative results were obtained in nineteen. Barium enemas, in twenty-eight patients, gave negative results in seventeen, and evidence of an extrinsic mass in eleven. Of the fourteen patients who had both an upper gastrointestinal series and a barium enema, only six had evidence of an extrinsic mass in both studies.

Eleven patients had negative results on both examinations. Six patients had only one study with a negative result in that one.

Clinical Diagnosis.—The difficulty in diagnosis is shown by the fact that a clinical diagnosis was made only twelve times in the entire series, and this after a prolonged hospitalization. In a further attempt to find some means of earlier diagnosis, analysis of these twelve cases was undertaken.

The age range was from 28 to 72 years, with all but four patients being between 45 and 65. Eleven were men, which is in accordance with the previously noted sex incidence of the disease. Seven were Negro and five white. The chief complaint, either a mass or pain in the abdomen, pointed more directly to the area of pathology than did the multitude of complaints listed for the group as a whole. The duration of complaints, the incidence of jaundice, and the presence of a mass were all comparable to the larger series. A cirrhotic history was elicited in only one patient. A palpable liver in all cases and liver tenderness in four suggest more extensive disease than the remainder of the series. Evidences of portal obstruction were found in three patients.

Serum bilirubin was abnormal in 80 per cent of those examined, cephalin flocculation in 45 per cent, thymol turbidities in 83 per cent. Bromsulphalein tests and Wassermann tests were each positive in one-third of the cases. Hematologic studies were not abnormal in any.

Upper gastrointestinal or barium enema x-ray studies demonstrated an extrinsic mass in seven patients, while three patients had entirely negative roentgen studies. Gall bladder x-ray films were not made for any of these patients.

Laboratory results and x-ray films indicated more advanced disease in this group, and therefore the diagnosis should have suggested itself more readily.

Surgery was performed in seven, with the only partial hepatectomy of the series being in this group.

O. H., a 54-year-old Negro man, was admitted with a chief complaint of a mass in the stomach for six months. There had been a 25-pound weight loss, inconstant pain in the right upper quadrant. Other findings were: nodular liver, icterus index 26, thymol 6.3, negative cephalin flocculation, proteins 8.25, red blood count 5.5 million. Barium enema and upper gastrointestinal series showed an extrinsic mass. At operation a large mass involving the left lobe of the liver was found and removed. The postoperative course was fairly smooth, and the patient was discharged six weeks after admission. Unfortunately, no follow-up is available.

Survival from the time of diagnosis was known in seven cases: one and two days; one, two, and three weeks; and two and three months. Thus the

prognosis in those where the diagnosis was made on clinical grounds would appear to be so poor as to make a clinical diagnosis of little value. Nevertheless, the infrequent suspicion of the diagnosis preoperatively suggests that many patients were unnecessarily submitted to prolonged hospitalization and investigation prior to a definitive diagnosis.

In addition to twelve cases diagnosed clinically, the correct diagnosis was established by surgical intervention with biopsy in twenty-one cases. The remaining twenty-four were not correctly diagnosed until autopsy. For almost any year during the study, the ratio of surgical diagnoses to autopsy diagnoses remains relatively constant at about one to one. Exploration was undertaken in thirty cases with a definitive diagnosis in each case. Peritoneoscopy with biopsy was performed only twice. Liver biopsy (punch or aspiration) was made in eleven patients (including the two with peritoneoscopy), five of whom subsequently had surgery. The pathology report on the liver biopsy did not agree with that obtained at surgery in any case.

TABLE VIII. ADDITIONAL CLINICAL DIAGNOSES

Liver		**33**	**Gall bladder**		**12**
Cirrhosis	16		Cholecystitis	7	
Tumor	5		Ca	3	
Ca, probably metastatic	2		Possible hydrops	1	
Toxic hepatitis	2		Cholelithiasis	1	
Possible Ca	2		**Lung**		**6**
Abscess	1		Right effusion	3	
Yellow atrophy	1		Ca, liver metastases	1	
Possible superimposed hepatoma	1		Lobular pneumonia	1	
Possible gumma	1		Possible pneumonia	1	
Hepar lobatum	1		**Kidney**		**4**
Weil's disease	1		Hypernephroma	1	
Stomach		**16**	Pyelonephritis	1	
Ca, liver metastases	5		Wilms's tumor	1	
Ca	4		Ectopic adrenal tissue attached to right kidney	1	
Peptic ulcer	3		**Retroperitoneal space**		**4**
Gastritis	1		Sarcoma	2	
Antral lesion by x-ray film	1		Possible abscess	1	
Ulcer	1		Abdominal aneurysm	1	
Ca pylorus, liver metastases	1		**Prostate**		**2**
Bowel		**13**	Ca, with metastases	2	
Gastrointestinal malignancy, liver metastases	5		**Ovarian cyst**		**1**
Ca colon	5		**Omental cyst**		**1**
Ca bowel	1		**Bladder tumor**		**1**
Healed duodenal ulcer	1		**Miscellaneous**		**16**
Ca rectum, liver metastases	1		Chronic amebiasis	4	
Pancreas		**12**	Porphyruria	2	
Ca	7		Metastatic Ca	2	
Pancreatic cyst	2		Malnutrition	2	
Acute pancreatitis	1		Each of the following:	1	
Ca?	1		Hematoma of abdominal wall, mild cystitis, neurocirculatory asthenia, Banti's disease, serofibrous peritonitis, edema of lower extremities		
Obstructed ampulla of Vater	1				

The utter confusion surrounding this condition is shown by Table VIII, listing those additional clinical diagnoses which pertained to the significant findings. The organs most commonly implicated were the liver, stomach, pancreas, gall bladder, and bowel. The diagnostic confusion was great enough

in twenty-nine patients to warrant careful abdominal exploration. Previous therapy had included programs for ulcer, amebiasis, malaria, cirrhosis, vitamin and iron deficiency, and general supportive therapy.

An extreme example of diagnostic confusion and difficulty was this case:

W. M., a 63-year-old Negro man, had a history of pain in the abdomen for two months and hematemesis for twelve hours. Stool was both black and bright red according to history. Physical examination revealed weight loss, liver tenderness, jaundice, a nodular liver, red-brown urine. The patient continued to vomit large quantities of blood, and in spite of transfusions died four days after admission. In the interim an icterus index of 23.4 was the only significantly positive finding, although serum proteins, prothrombin time, thymol turbidity, cephalin flocculation, and other studies had been made. At autopsy a hepatoma with invasion and obstruction of the portal vein was found, but there was also a small, bleeding peptic ulcer of the stomach, with massive gastrointestinal bleeding, and polyposis of the colon.

Another example of difficulty in diagnosis is the following case, which is doubly interesting because of the extensive work-up and the long period of observation prior to diagnosis:

J. B. L., a 63-year-old white man, was first admitted in May, 1947, with pain before meals, food relief, tarry stools, and jaundice for the week prior to admission. There was a six months' history of weight loss and abdominal tenderness. Gastrointestinal x-ray films, barium enema, and gall bladder studies were all negative. Diagnosis was peptic ulcer. The next admission was in July, 1950, with pain following meals, nausea, but no vomiting or tarry stools. Again there was weight loss and mid-epigastric soreness. The diagnoses were peptic ulcer and gastritis. The same three sets of x-ray films were again negative. In July, 1951, the patient was admitted with epigastric pain, nausea, vomiting, and melena. Weight loss was 28 pounds. Stools were clay colored, tarry, and bloody at intervals. There was weakness, tinnitus, pain below the nipples bilaterally. Physical examination revealed an emaciated, jaundiced man, with liver tenderness, and a hard mass filling the entire upper abdomen. Complete blood count, bleeding time, clotting time, urine, cholecystogram, barium enema, and upper gastrointestinal series were all negative. Exploration revealed one large mass about the size of a chicken egg in the left lobe of the liver and numerous hard areas throughout the liver. Pathology report was hepatic cell-type carcinoma. The postoperative course was uneventful. The patient was admitted three months later in a terminal, jaundiced, irrational state.

Eighteen patients who had an ante-mortem diagnosis were traced to the time of death. Four patients survived less than forty-eight hours after the diagnosis was made, and at the other extreme, one patient survived one year. All others survived less than three months, with a median survival of three weeks. This emphasizes the importance of a thorough attempt at earlier diagnosis, with early abdominal exploration in all suspected cases. It is by no means certain that all of these cases would be amenable to surgery at any time, but it is reasonable to believe that at least some of them might start as unicentric lesions and be amenable to surgery while still relatively localized. If these patients are to be helped, and they are the only ones who can be helped, they must be explored earlier than the present group was. If a lesion begins as a multicentric carcinoma, involving all portions of the liver, obviously such a patient is never a candidate for curative surgery.

Cholangiocarcinoma.—Since there were only five patients with a diagnosis of cholangiocarcinoma, differences between this group and the over-all series were studied.

There was only one Negro patient in the group. The chief complaints in this group were abdominal pain, cough, or abdominal swelling. Weight loss and jaundice, detected in all but one patient, were more prominent in the history than in the over-all series. The liver was palpable in each case, extending as much as seven fingers below the costal margin in one. The liver edge, smooth in two and nodular in two, was similar to that in the over-all group. None of these patients had an associated cirrhosis, whereas in the thirteen patients who did have cirrhosis, the primary type of carcinoma was a liver cell type in every instance.

From the few cases available, cholangiocarcinoma appears to be more common in the white than in the Negro race, and is more common in the male than in the female. The duration of symptoms would seem to be shorter than that in the over-all group, and the symptoms point more directly to the area of involvement. A history of weight loss and jaundice were more prominent. Changes in the urine and stool were less frequent than in the group as a whole. The liver was uniformly palpable, which is in line with the greater predominance of right upper quadrant symptoms. The tremendously elevated van den Bergh test and icterus index values, the highly positive flocculation tests, and the marked Bromsulphalein retention were not as common in the cases of cholangiocarcinoma as in the over-all series. The hemoglobin, red and white count values are even closer to the normal range in this group than in the over-all group.

Metastases were found in three of these patients. The survival time, known in two, was approximately two weeks from the first visit of the patient.

Of the twelve patients in whom a diagnosis was made clinically, three were in the small group with cholangiocarcinoma, which is further confirmation of the fact that these patients are being seen at a much later stage, when the clinical diagnosis should be easier to establish.

Coexisting Cirrhosis.—Cirrhosis is commonly thought to play some role in the development of primary cancer of the liver. Since a coexisting cirrhosis would enhance the diagnostic difficulties, these patients were further analyzed.

The diagnosis of cirrhosis was made in only thirteen patients in this entire series. This is in direct contrast to most reported series since the incidence of cirrhosis is usually thought to vary from 25 per cent to 90 per cent. Since clinical diagnosis has not been used in this series and since adequate histologic sections were available in all cases, the failure to make the diagnosis of cirrhosis more frequently cannot be explained on the basis of insufficient study of any case. We are at a loss to explain why the additional diagnosis of cirrhosis was made only once without benefit of autopsy. Thus cirrhosis was found in approximately 50 per cent of those patients autopsied, but the over-all incidence, which we consider reliable, was only 23 per cent.

The average age of these patients and the white-Negro distribution were about the same as for the entire series. The following items were found with approximately equal frequency in the patients with coexisting cirrhosis and the larger group: the variety of chief complaints, evidences of weight loss

and jaundice, an alcoholic history, change in the color of the urine, pain location and type, cephalin and thymol tests, relatively normal hemoglobin, red and white counts.

Significant differences between the two groups were found in the greater duration of complaints in the group with coexisting cirrhosis, the median value being one month longer than for the entire series. The presence of a mass in only two of these patients in contrast to 81 per cent of the entire group may be related to the later stages of cirrhosis with the accompanying decrease in the size of the liver. However, the presence of edema in a relatively small per cent of these patients is somewhat surprising. Changes in the color of the stools were less frequent here.

TABLE IX. DIFFERENCES BETWEEN CASES WITH MALIGNANCY ALONE AND MALIGNANCY PLUS CIRRHOSIS

	CIRRHOSIS PLUS MALIGNANCY	MALIGNANCY ALONE
Duration	Longer	
Mass	15%	81%
Edema	38%	65%
Change in stool	30%	55.9%
Liver palpable	46%	90%
Liver tender	30%	54.8%
Liver nodular	23%	50%

The liver was palpable, tender, and nodular in fewer patients than in the larger series. The van den Bergh test was consistently positive, with 60 per cent of all values over 4 being found in this group. Similarly, 50 per cent of all icterus index values over 30 were in this small group. The Bromsulphalein retention was significantly elevated (20, 25, and 48 per cent) and indicates the severe liver damage in those patients with a combination of cirrhosis and malignant disease.

Thus, cirrhosis was present in less than one-fourth of the entire series. In those patients with both processes, the duration of symptoms was slightly longer and the male sex was strongly predominant. History and physical examination were not significantly different from the group as a whole, except for the infrequent presence of a mass here. When both conditions were present, the van den Bergh test, icterus index, and Bromsulphalein tended to be significantly higher. Even though many of these patients were explored, the diagnosis of cirrhosis tends to be made only with full autopsy, when a primary cancer of the liver is present.

Autopsy.—Autopsy was performed in twenty-six cases.

Twenty-three patients had metastases to forty-three sites, most frequently to the chest, peritoneum, lymph nodes, specific organs, and blood vessels.

In addition to the primary lesion and its metastases, there were numerous other autopsy findings which may explain some of the clinical confusion, and which may have complicated any attempts at proper diagnosis or therapy. The organs most commonly involved by other conditions were the lungs, liver, peritoneum, and spleen. Almost every organ in the body was involved in this

study, and the very fact that multiple conditions existed in so many cases makes one wonder if a proper ante-mortem diagnosis could be made in some cases.

TABLE X. METASTASES

Chest		13	Specific organs		5
Lungs	9		Spleen	1	
Pleural space	2		Adrenals	2	
Chest wall	2		Thyroid	1	
Peritoneum		9	Kidney	1	
Peritoneum	3		Vascular system		4
Cul de sac	2		Portal vein	1	
Mesentery	2		Superior mesenteric vein	1	
Omentum	1		Splenic vein	1	
Parietal peritoneum	1		Inferior vena cava	1	
Lymphatics		7	Generalized carcinomatosis		2
Retroperitoneal nodes	1		Bone		1
Regional nodes	2		Lumbar vertebra, bone marrow		
Neck nodes	1		Hepatic duct		1
Periaortic nodes	1		Total		42
Abdominal and thoracic periaortic	1				
Celiac, and left supraclavicular	1				

TABLE XI. ADDITIONAL AUTOPSY DIAGNOSIS

Lung		40	Spleen		10
Bilateral atelectasis	7		Congestive splenomegaly	6	
Bronchopneumonia	4		Multiple infarcts	1	
Pulmonary edema	4		Old perisplenitis	1	
Pleural effusion	4		Congestion, dilation splenic sinusoids	1	
Pulmonary emphysema	4		Acute splenic tumor	1	
Pulmonary congestion	3		Kidney		4
Metastases to both lungs	3		Benign nephrosclerosis	2	
Multiple infarcts	2		Solitary cyst	1	
Congestion and hemorrhage	2		Infarct	1	
Metastases to right pleural space	1		Stomach		2
Tumor thrombus, both lungs	1		Atrophic gastritis	1	
Each of the following:	1		Bleeding small peptic ulcer	1	
Fibrous pleuritis, caseous tuberculosis, right hydrothorax, hemorrhage and necrosis of metastatic nodules, hemorrhagic bronchitis			Esophagus		2
			Varices	2	
Liver		17	Adrenal adenoma		2
Jaundice	8		Pancreas		2
Portal cirrhosis	4		Chronic pancreatitis	1	
Laennec's cirrhosis	3		Interstitial pancreatitis	1	
Hepatomegaly	1		Colonic polyps		2
Fatty metamorphosis	1		Prostatic hypertrophy		2
Peritoneum		12	Pituitary		1
Ascites	5		Posterior lobe eosinophilic infiltration		
Bloody fluid	3				
Upper abdomen filled with mass	1				
Abscess	1				
Hematoma between liver and diaphragm due to tumor	1				
Mesenteric lymphadenopathy	1				

SUMMARY

Primary cancer of the liver continues to be a difficult diagnostic problem. A poor prognosis will be an integral part of the diagnosis as long as the diagnostic acumen remains at the low level suggested by this study.

Awareness of the disease, and a more earnest attempt to diagnose the more obscure cases will be necessary before any improvement in the present picture can be attained.

This is predominantly a disease of males. It affects both white and Negro. The history can be as varied as any in medicine, particularly in the earlier stages. Neither an alcoholic, a cirrhotic, nor a syphilitic history is necessary. Liver function tests may show only the slightest deviation from the normal, and hematologic studies in general will tend to be within normal limits, even in the presence of extensive hepatic pathology. Properly taken x-ray films of both the upper and lower gastrointestinal tract, with emphasis on displacement of the bowel by an extrinsic mass, should be a leading clue to the presence of intrahepatic pathology.

If these patients will be submitted to some earlier exploratory procedure, whether it be peritoneoscopy, liver biopsy, or exploratory laparotomy, then a greater per cent of diagnoses will be established at a time when there may be some hope and before the patients have been exposed to unduly long diagnostic surveys. If it be remembered that only a careful survey and an early diagnostic exploration can offer a better prognosis, then future studies can hope to show longer survivals.

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METABOLIC ALTERATIONS FOLLOWING EXPERIMENTAL VESICOSIGMOIDOSTOMY*

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THE cause of the chemical aberrations following ureterosigmoidostomy has been the subject of widespread discussion.[1-4] Various theories as to its etiology have been advanced, and the kidney has been both invoked and rejected as the causative agent.[5-7] In an effort to elucidate further the mechanism of the electrolyte disturbances attending ureteral transplant into the sigmoid colon, and with the aim of improving the management of such cases, a series of metabolic studies in animals was undertaken.

MATERIALS AND METHODS

Ten mongrel dogs weighing between 10 and 20 kilograms were utilized in this work. Four dogs died because of technical difficulties immediately postoperatively, and thus were excluded. In an effort to diminish the occurrence of pyelonephritis, and yet to produce a condition in the experimental animal paralleling the clinical state of ureterosigmoidostomy, the bladder was anastomosed to the sigmoid colon after division and closure of the urethra.[8] The bowel was prepared for transplantation by giving 250 mg. of Aureomycin four times a day for two days and enemas daily. Preoperatively the concentrations of sodium, potassium, and chloride in the plasma were determined along with the hematocrit,[9] urea nitrogen,[10] carbon dioxide content,[11]† and pH of the whole blood.[12] Repeat determinations were secured during an initial postoperative observation period of three weeks, during which time metabolic processes had become more or less stabilized. The experimental course was then arbitrarily divided into various periods during which fixed amounts of ammonium chloride, sodium bicarbonate, anion-exchange resins, and glutamic acid were added separately, at intervals, to a controlled constant diet. Observations were also made during periods of dehydration and starvation. Similar chemical determinations to those done during the immediate postoperative period were made on the blood obtained from the animals throughout the course of the experiment.

A standard diet was fed the animals throughout the study and they received water ad libitum. A low-residue diet was used to ensure ease of col-

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†The CO_2 content of whole blood was measured in this study, since the same blood sample was used for this determination as for the evaluation of the blood pH. The CO_2 content of whole blood is modified by changes in the hematocrit but in general, it mirrors the CO_2 content of plasma.

lections in metabolic cages. Electrolytes were added to the daily diet* so that it contained 50 meq. of sodium, 50 meq. of chloride, and 7 meq. of potassium per dog per day regardless of the amount of standard diet given. The study periods were divided as follows:

A. *Ammonium Chloride.*—To the previously described standard diet, 1.5 to 2 Gm. of ammonium chloride (28 to 37.4 meq. of chloride) was added for two days. Accurate dosage was secured by manual feeding of tablets (enteric-coated).

B. *Sodium Bicarbonate.*—Similarly, a fixed dose of 5 Gm. (59.5 meq.) of sodium bicarbonate was added to the diet daily for four to seven days. Two of the animals received bicarbonate for seven days while the remaining dogs during the last three days received the standard diet without added salt.

C. *Glutamic acid* was added to the diet in doses of 1 Gm. per day for four to nine days.

D. *Anion-exchange Resins*†.—Two types (Dowex-2 and 3) were given orally in doses of 15 Gm. a day for one week. The first resin was in the free base form and the second was given as the bicarbonate salt.

E. *Dehydration.*—All four experimental animals were subjected to twenty-four-hour periods of total restriction of fluid intake. Subsequently, two animals were limited to inadequate fluid intake for twenty-four hours, followed by complete restriction for a subsequent twenty-four hours. Throughout this period the basal diet was offered daily.

F. *Mercuhydrin.*—One dog received Mercuhydrin 0.5 ml. intravenously per day for three days.

Fluid intake and output were measured daily. The animals' weights, hematocrits, and aforementioned blood or plasma chemistries were determined at the beginning of each period of the metabolic study. All excreta were collected and measured. The amount of sodium, potassium, and chloride in both the diet and excreta for representative twenty-four-hour periods was determined, and balance studies for these days were completed. The concentrations of sodium, potassium, and chloride were studied in both voided specimens (which may be pooled for varying lengths of time in the colon) and those obtained by rectal tube where the contact with the absorbing surface of the colon is minimal. This was done in order to evaluate the effect of the contact of urine with the colonic mucosa, since it has been shown[5] that significant amounts of chloride and nitrogenous waste materials may be absorbed in this fashion.

Measurements of the sodium and bromide space along with the plasma volume were undertaken by the use of Na^{24}, Br^{82}, and iodinated albumin (I^{131}) during control periods and following dehydration.[13, 14] Intravenous pyelograms were obtained on all animals at the termination of their metabolic study.

*Diet consisted of 25 per cent casein, 18 per cent lard, 7 per cent butter, 25 per cent sucrose, 22 per cent cracker meal, 2 per cent Brewer's yeast, 1 per cent bone ash. This mixture was equivalent to 5.2 calories per gram and the dogs received 250 to 300 Gm. per day depending on size. Minerals (2.37 Gm.) were added per day consisting of 44 per cent calcium lactate, 44 per cent magnesium citrate, and 12 per cent ferrous citrate. The diet was fortified with vitamins A and D.

†Supplied through the courtesy of the Dow Chemical Company, Midland, Michigan.

RESULTS AND COMMENTS

Observations During the Immediate Postoperative Period.—The six animals which survived the operative procedure were followed over a period of two to three weeks by repeatedly determining plasma concentrations of electrolytes. At the end of this period, the blood values seemed to have stabilized. Determinations were made at three- to four-day intervals, and the changes which occurred in representative animals appear in Fig. 1.

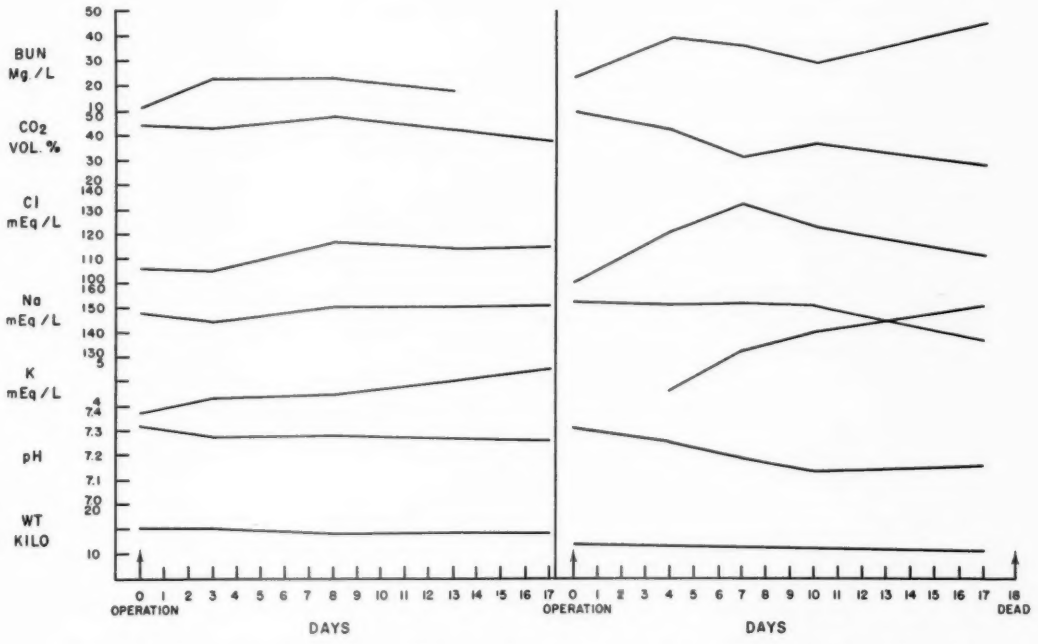

Fig. 1.—Comparison of immediate postoperative periods. Left graph shows changes occurring in a representative animal which survived the period of adjustment. Right graph shows changes occurring in an animal which died of starvation and electrolyte depletion.

The blood urea nitrogen rose within three days following operation in all six dogs, remained elevated for approximately one week, then returned to the preoperative level. Boyce[8] noted this same initial elevation and eventual return to normal of the blood urea nitrogen concentration in dogs with vesicosigmoidostomies. The reason for this transient elevation of the blood urea nitrogen, observed in our experiments as well as in his, remains somewhat obscure. A similar elevation immediately postoperatively has been observed in patients who have undergone ureterosigmoidostomies. Elevations of the blood nitrogenous products may take place following other operative procedures and might be explained, in many instances, by the increased catabolism of body proteins and reduction in urinary flow. This reduced flow is not dependent upon impaired renal function. More frequently it results from pituitary-adrenal hyperfunction, an accelerated insensible fluid loss with a low fluid intake, transudation of fluid and salts into the operative site, or combinations of these factors.

The rise in the plasma chloride and fall in blood CO_2 content occurred concomitantly, with the maximum change being reached between four and ten days postoperatively. The fall in blood pH paralleled the appearance of the hyperchloremia. Sodium and potassium levels remained essentially unchanged at the end of the three-week observation period.

Two of the six dogs died at the end of the three-week observation period. Although their immediate postoperative plasma electrolytes and urea were similar to those of the other four dogs, these animals refused all food and would take only water. Eventually their blood values changed in a manner characteristic of hyperchloremic acidosis. The alterations will be discussed later in relation to the subject of starvation.

Observations During Experimental Periods.—Each of the four dogs which survived the three-week postoperative period was placed on the control diet, and studies were carried out at intervals over the following four months. During this entire period all the animals lost weight. The average weight loss amounted to 13 per cent of their control weight, the maximum being 16 per cent, and the minimum 7.5 per cent. The blood urea nitrogen remained stationary or returned to normal preoperative levels following transient variations. Similarly, the hematocrit remained essentially unchanged. At the end of the period of study, intravenous pyelograms were made and showed prompt excretion of the dye within thirty minutes and no evidence of hydronephrosis. In thirty-three dogs on which Boyce[8] had performed vesicosigmoidostomy, none showed evidence of pyelonephritis or hydronephrosis at autopsy.

Aside from these general statements, the remaining observations dealing with volume of fluid intake and output, electrolyte balance, and plasma levels must be considered together with the individual type of treatment because other factors such as appetite, thirst, diarrhea, and diuresis have modified the production of acidosis. For this reason, metabolic charts (Figs. 2 to 5) for each dog are utilized to correlate all these factors. In these figures the intake is plotted from the zero line upward and the output (urine and feces) is plotted from the top of the intake column downward. Positive balance is represented by the solid black areas above the zero line, and extension of the column below the zero line designates negative balance. Between experimental periods where no analysis of excreta was made, the intake is plotted in broken lines. The levels of plasma sodium, potassium, and chloride are listed at intervals above the respective balance columns.

The effect of administering sodium bicarbonate: All four animals received a supplement of 5 Gm. of sodium bicarbonate (59.5 meq.) a day in addition to 50 meq. of sodium and chloride in their standard diet. After three or four days the dietary sodium chloride was withdrawn and the supplement of 5 Gm. of sodium bicarbonate was continued. During this latter period plasma sodium levels remained unchanged. The sodium balance became positive or, in the case of previous negative balance, became less negative. The plasma potassium levels fell and the potassium balance tended to show a smaller negative balance, or to become positive. The blood CO_2 content approached normal. The

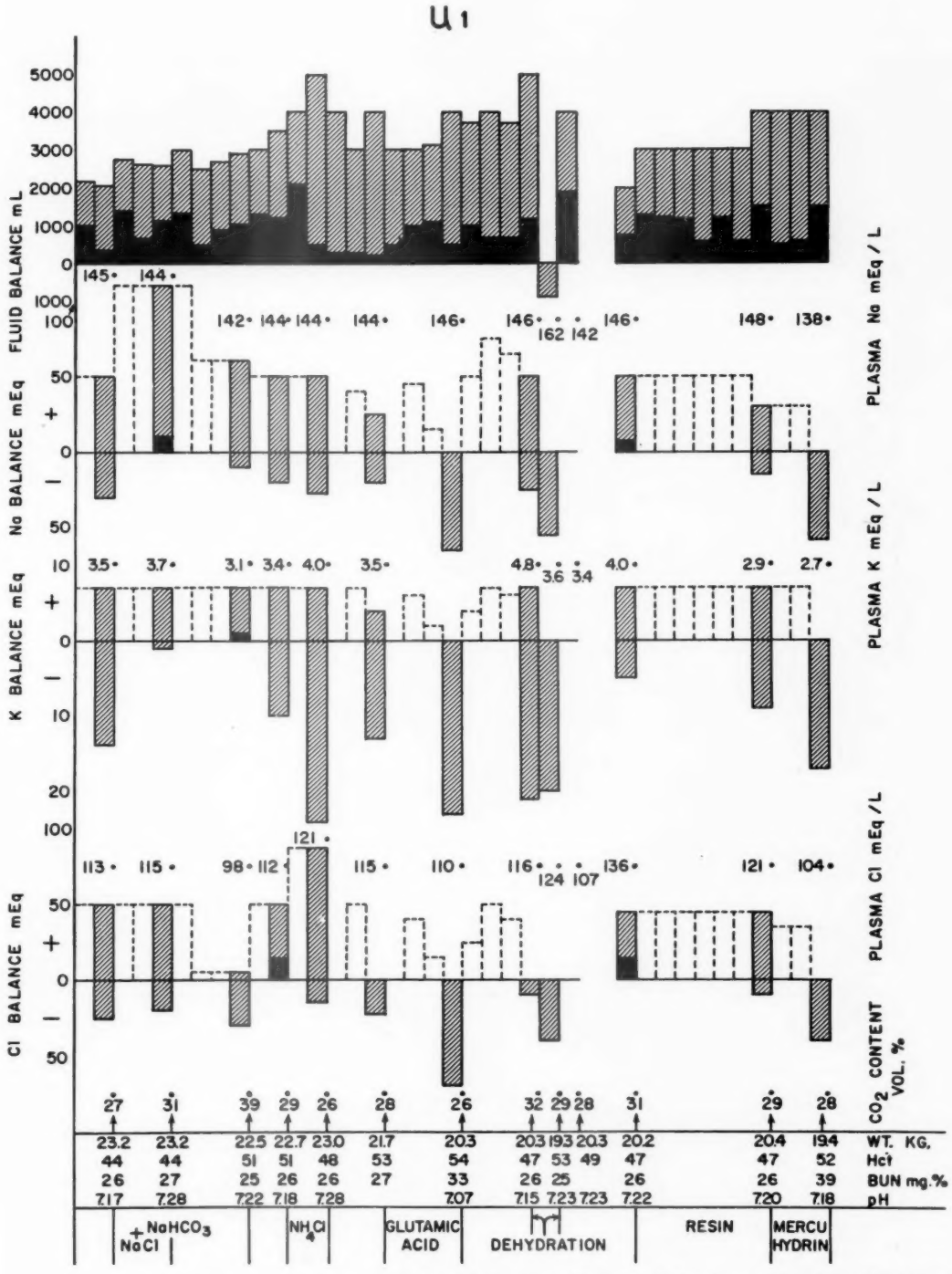

Fig. 2.—Changes in fluid and electrolyte balance in Dog U1 following vesicosigmoidostomy. In the metabolic charts the intake is plotted upward from the zero line and excretion is plotted from the top of the intake column downward. The solid black areas represent positive balance and the extension of the columns below the zero line designates negative balance. The areas enclosed in the broken lines between experimental periods represent only the intake since excreta were not collected during this time.

plasma chloride fell slightly in these short-term experiments and showed a greater decrease toward normal when the chloride ion was restricted from the diet. In a similar study[15] on patients, which will be reported subsequently,

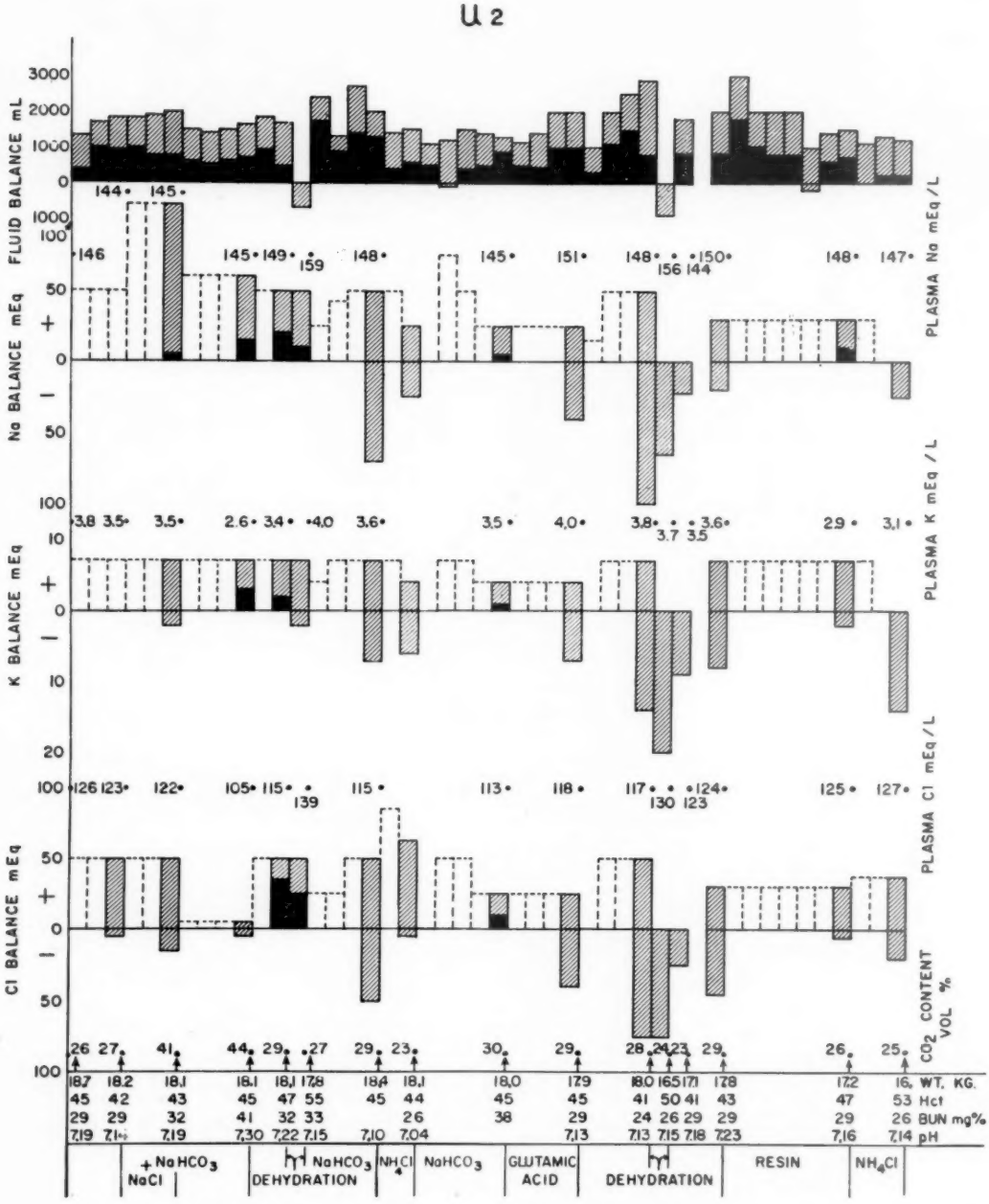

Fig. 3.—Changes in fluid and electrolyte balance in Dog U2 following vesicosigmoidostomy.

the administration of 70 meq. of sodium bicarbonate and 30 meq. of potassium citrate did result in eventual lowering of plasma chloride concentration, although the patient continued to take 100 meq. of sodium and chloride per day.

In three of the four animals, chloride balance became even more negative in the face of the chloride restriction. The pH rose with the correction of the acidosis. The large negative chloride balance reflects the loss of the excessive,

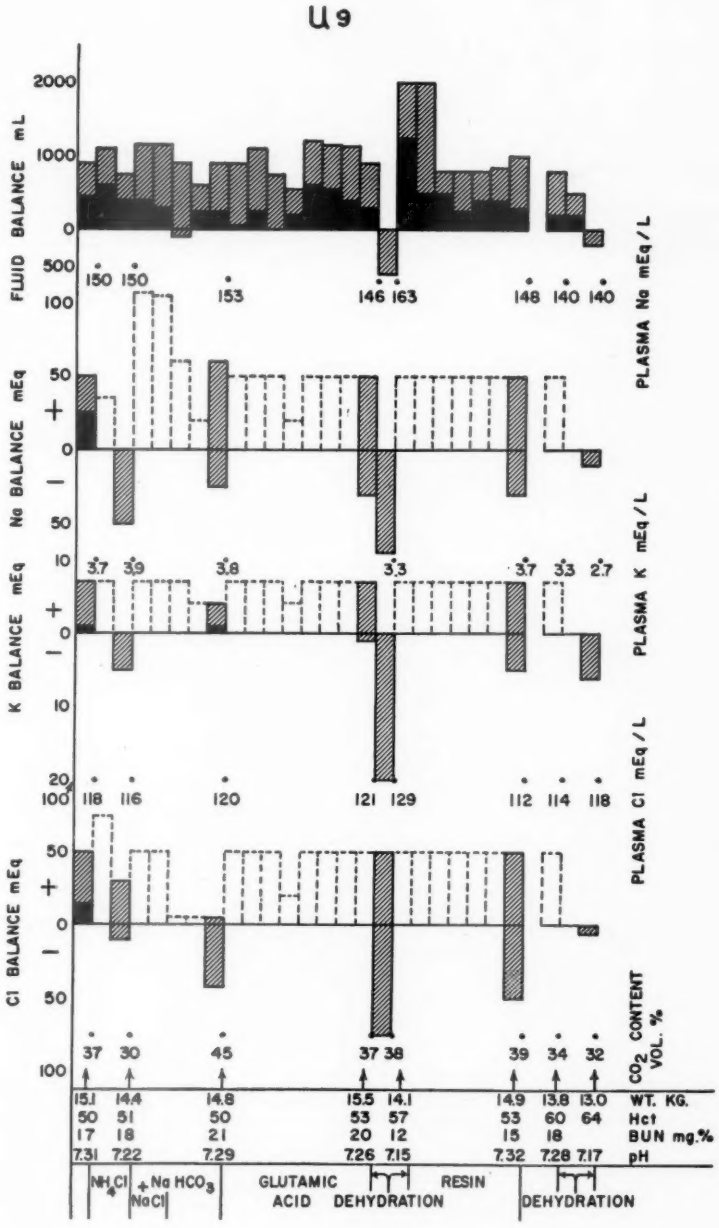

Fig. 4.—Changes in fluid and electrolyte balance in Dog U9 following vesicosigmoidostomy.

accumulated chloride from the body and undoubtedly would have diminished when the chloride concentration of the plasma became normal (renal chloride conservation would then occur).

Comparison was made between excreta obtained by rectal tube at the end of the overloading period with excreta that was voided during the last twenty-four hours of the same period (Table I). At the end of the phase of overloading with sodium bicarbonate, the concentrations of sodium and chloride were

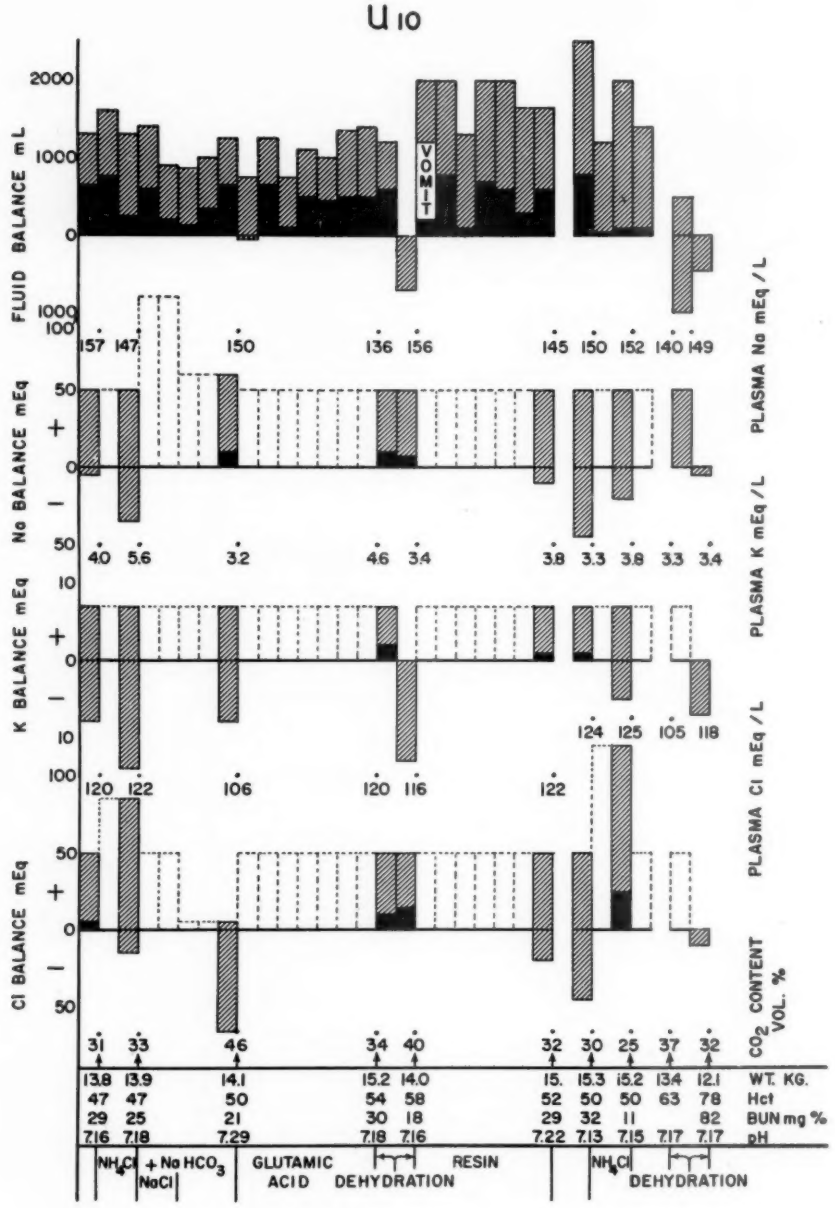

Fig. 5.—Changes in fluid and electrolyte balance in Dog U10 following vesicosigmoidostomy.

higher in the urine voided than in the specimens obtained from the rectal catheter. The values of potassium in both specimens were the same in two dogs and higher in the tube specimen in the remaining two dogs.

From these observations the conclusion is reached that if an excess of fixed base over chloride is provided, the acidosis will be corrected. Not only was the sodium balance restored during such periods, but a favorable change in the potassium balance also occurred. Since the serum potassium fell while potassium was being retained, the potassium ion must have returned to the intracellular compartment. That this shift takes place with the correction of acidosis has been suggested by others.[16]

TABLE I. COMPARISON OF ELECTROLYTE CONCENTRATIONS OF EXCRETA OBTAINED BY RECTAL TUBE AND BY VOIDING

PERIOD	ANIMAL	SODIUM (MEQ./L.)		POTASSIUM (MEQ./L.)		CHLORIDE (MEQ./L.)	
		TUBE	VOIDED	TUBE	VOIDED	TUBE	VOIDED
Postoperative period	U1	51.5	29.0	10.5	9.5	31.5	24.0
	U2	44.0	61.0	11.0	10.0	50.0	53.5
	U9	9.0	30.0	13.5	17.0	10.0	22.0
	U10	51.0	57.5	27.0	23.0	50.0	50.0
Sodium bicarbonate	U1	50.0	62.5	4.5	5.0	31.0	46.0
	U2	49.0	83.0	7.5	8.0	29.5	54.5
	U9	101.0	146.0	12.0	5.0	40.0	49.5
	U10	48.0	82.0	23.0	22.0	74.0	99.0
Ammonium chloride	U1	44.0	12.0	14.0	7.0	43.5	22.5
	U2	19.0	27.0	12.0	14.0	39.0	59.0
	U9	52.0	64.0	34.0	23.0	75.0	86.0
	U10	42.0	30.0	14.0	11.0	30.0	47.0
Glutamic acid	U1	39.5	19.0	11.0	9.5	24.0	19.0
	U2	64.0	66.0	11.0	11.5	47.5	62.0
	U9	97.5	49.0	13.5	14.5	90.0	124.5
	U10	71.5	57.0	8.5	9.0	61.5	67.5
Resin	U1	39.0	20.0	12.5	11.5	35.0	23.0
	U2	38.0	47.0	10.0	14.0	61.0	63.0
	U9	72.0	107.5	14.0	18.0	86.5	139.0
	U10	45.0	56.5	7.5	4.0	57.0	66.0
24-Hour dehydration	U1	16.0	54.0	5.0	21.0	22.0	46.0
	U2	74.0	69.0	29.0	81.0	89.5	84.0
	U9	39.0	115.0	23.0	38.0	13.0	94.0
	U10	–	52.0	–	24.0	–	42.0
48-Hour dehydration	U9	12 5	8.0	22.0	29.0	11.0	2.5
	U10	8.0	8.5	33.5	16.0	3.0	6.0
Mercuhydrin	U1	29.0	13.0	8.5	8.0	19.0	17.5

Although the blood CO_2 became elevated upon administration of sodium bicarbonate, the plasma chloride often did not fall significantly until there was a restriction of chloride intake in these short-term experiments. This suggests an independence of chloride ion absorption from the colon, even in the presence of adequate bicarbonate ion. We confirmed this by the use of radioactive isotopes in solutions placed in isolated segments of colon.[17] In the face of dietary chloride restriction, only one dog showed a tendency toward chloride retention. In other words, in three animals with restricted chloride intake, excretion of chloride at least temporarily was enhanced by the administration of sodium bicarbonate. Inasmuch as chloride is thought not to

enter the cell, this excreted chloride must have been derived from the interstitial and vascular compartments. It is excreted along with the excess sodium (or fixed base) and undoubtedly would eventually be conserved if the period of chloride restriction was continued and an excess amount of fixed base was not being given.

Overloading with ammonium chloride: The production of hyperchloremic acidosis by ureterosigmoidostomy has been likened to the acidosis produced by the administration of ammonium chloride.[7] Therefore the effects of overloading with ammonium chloride for a two-day period were studied.

Plasma sodium levels remained unchanged with one exception (Fig. 2) where a fall was noted when the animal stopped eating (reduced sodium intake) and acidosis developed. During ammonium chloride administration the sodium balance became increasingly negative with one exception (Fig. 5). The loss of sodium under such circumstances would be expected since the administration of ammonium chloride initially depletes the body of sodium.[18] In these animals with vesicosigmoidostomies a loss of sodium as evidenced by a negative sodium balance is not accompanied by a drop in the plasma sodium level. It was not possible to maintain these animals on prolonged administration of ammonium chloride, for with enhancement of the acidosis the animals refused to eat and introduced the effects of an inadequate intake.

Examination of voided excreta compared to excreta obtained by rectal tube at the end of the period of ammonium chloride administration revealed higher sodium concentrations in the tube specimen than in the voided specimens in two dogs with adequate sodium intakes, indicating some reabsorption of sodium from the colon. A reversal of the findings occurred in the two other dogs which had a reduced sodium intake because they stopped eating. In the face of an inadequate intake, the plasma sodium level fell slightly in one dog and remained essentially the same in the other dog, while the voided excreta of both animals contained more sodium than did the tube specimen.

Plasma potassium levels remained essentially unchanged, and potassium balance became slightly more negative during the administration of ammonium chloride. Three of the four dogs showed a greater potassium concentration in the tube excreta as compared with the voided specimens. The remaining dog showed only slight differences in the two specimens. As acidosis develops, potassium is thought to leave the cell. To maintain the normal plasma potassium level, more potassium is excreted, causing the potassium balance to become negative.[16]

Upon administering ammonium chloride, the blood CO_2 and plasma pH decreased and the chloride level increased. During such periods the degree of negative chloride balance increased on four occasions and diminished or became positive on two occasions. Three dogs showed more chloride in the voided excreta than in the tube excreta. In one animal the reverse was true. Therefore the significant findings here are that large amounts of chloride are presented to the colon and the amount of reabsorption is reflected in the plasma chloride level.

The administration of glutamic acid: The role of ammonia in the maintenance of the hyperchloremic state has been discussed by certain authors.[6] Since glutamine yields urinary ammonia,[19] and there is an equilibrium between glutamic acid and glutamine, attempts were made to increase the amount of ammonia available in the colon by feeding glutamic acid. Two animals received 1 Gm. of glutamic acid orally per day for five days and two others received it for seven days.

During the course of glutamic acid administration there was no significant change in fluid balance. Neither was there a consistent change in the serum levels of sodium, potassium, chloride, or blood CO_2. The blood pH fell slightly in three dogs, suggesting metabolic or starvation ketosis, and the blood urea nitrogen rose slightly. Sodium, potassium, and chloride balances were negative, which probably reflects the reduced food intake accompanying the administration of this substance.

Comparison of sodium, potassium, and chloride levels in voided and tube specimens showed little difference as compared with values obtained during the period of postoperative adjustment. Three dogs did show higher concentrations of sodium in the tube specimen than in the voided sample. Possibly this is due to the negative sodium balance resulting from reduced food intake and an attempt by the animal to reabsorb as much sodium from the colon as possible.

Administration of anion-exchange resins: Anion-exchange resins were administered in an attempt to extract chloride from these animals. Two different anion resins were administered in the dosage of 15 Gm. a day to the animals.

No significant change was found in fluid balance, plasma values of sodium, potassium, chloride, blood CO_2, and pH which could be directly attributed to the resin. No real change occurred in the balance of sodium or potassium. Other investigators[6] have also failed to show any significant advantage in the use of anion-exchange resins in the treatment of hyperchloremic acidosis, since resins that are available at present bind chloride efficiently at an acid pH but lose it in more alkaline solutions, for example, the lower bowel. Whether they have any protective value in allowing more freedom of diet has not been determined by our short-term experiments.

Dehydration: All four dogs had a much larger intake of fluid postoperatively than they did preoperatively or than do normal healthy dogs. Postoperatively the larger animals, weighing approximately 20 kilograms, would take between 2 and 4 L. of water daily, and the smaller dogs, weighing about 10 kilograms, would take between 1 and 2 L. of water or amounts equaling roughly twice the volume consumed when they were normal. This increased fluid intake is beneficial, since it leads to a lower urinary concentration of chloride, a more rapid evacuation, and hence a reduced absorption.

The most profound changes occurring during this series of experiments were brought about by water deprivation. Certainly, the greatest change in the clinical course of the animals occurred during such periods. Deprivation of water was accompanied by extreme thirst, anorexia, and extremely rapid development of electrolyte imbalance. Two dogs were observed for forty-

eight hours after receiving only 500 ml. of water at the onset of this period. Both dogs were greatly dehydrated with elevated hematocrits, and in addition one showed a marked collapse of the peripheral veins. It is significant that the latter dog showed the only marked but transient rise in blood urea nitrogen levels during the entire series of experiments.

Sodium and bromide spaces were determined after four and five hours of equilibration, and plasma volumes (ten-minute sample) were obtained in two dogs by using Na^{24}, Br^{82}, and radioactive iodinated (I^{131}) albumin, respectively. Control values were obtained and the determinations were repeated after the same two dogs were subjected to a twenty-four-hour and then a forty-eight-hour period of water deprivation. The results appear in Table II.

TABLE II. SODIUM AND BROMIDE SPACE AND PLASMA VOLUME IN NORMAL AND DEHYDRATED DOGS

	PLASMA VOLUME				Na^{24} SPACE				Br^{82} SPACE			
	DOG U1		DOG U2		DOG U1		DOG U2		DOG U1		DOG U2	
	ML.	%	ML.	%	ML.	%	ML.	%	ML.	%	ML.	%
Control	717	100	854	100	4,583	100	5,200	100	4,080	100	4,920	100
24-Hour dehydration	628	88	789	93	3,508	77	5,105	88	4,130	101	4,675	95
48-Hour dehydration	526	73	525	61	3,033	66	3,540	68	3,743	92	3,618	72

The greatest and most rapid changes seem to have occurred in the plasma volume. A reduction of 30 per cent and 40 per cent in the plasma volume took place in the forty-eight-hour period, and this was evidenced by a shocklike state in one dog. High plasma chloride concentrations and a diminution of the plasma volume and thiocyanate space to a similar degree have been reported when normal animals were given no food or water, but such changes were noted only after six to seven days.[20] Thus the much more rapid development of dehydration and acidosis must result from the accelerated water and electrolyte losses noted in our animals.

Diminution of the sodium space was greater than that of the bromide space. If the assumption is made that the bromide ion behaves in a manner similar to the chloride ion, and that it does not enter the cell, the relative distribution of the bromide ion in the fluid compartments was evidently the least disturbed. One dog developed considerable diminution of the sodium space within twenty-four hours, and both dogs showed marked contraction of the sodium space in forty-eight hours.

In order to discuss these changes in physical distribution it is necessary to examine first the plasma electrolyte levels. All four animals were in marked fluid deficit. The blood CO_2 and pH fell, and the plasma chloride rose rapidly, the plasma sodium concentration increased to higher than normal values, and plasma potassium fell in every case. Balance studies revealed a marked negative balance of sodium, potassium, and chloride although the loss of these ions was less during the second day than that noted during the first twenty-four-hour period.

Comparison of concentrations of specimens of voided excreta and rectal tube excreta at the end of the period revealed significant difference in values

in two of the three animals in which data were obtained. There were considerably higher concentrations of sodium, potassium, and chloride in the voided specimens than in the tube specimens in twenty-four hours. At the end of forty-eight hours the concentrations of the various ions in both the tube and voided specimens were greatly reduced.

The changes that occurred during water deprivation are primarily a rapid enhancement of the acidosis and a loss of electrolytes and fluid. The decrease in body electrolytes is aggravated during acidosis by the accompanying anorexia and lack of an adequate electrolyte intake. Loss of sodium occurs because of the failure of reabsorption of this ion from the colon. With acidosis a shift of sodium into the cells occurs while potassium leaves the cell and is excreted. A rather marked loss of potassium was evidenced by a drop in plasma potassium, the negative potassium balance, and the increased potassium in both tube and voided excreta. The rise in plasma sodium in the face of a negative sodium balance and loss of this ion in the excreta are explained on the basis of a contracted extracellular fluid volume with a greater loss of water than sodium. Contraction of sodium space occurred, and while the amount lost was greater than the decrease in the plasma volume, the per cent change was not as significant. The reduction of the extracellular sodium fluid volume is dependent upon two major factors: an external loss of water and sodium and the migration of sodium intracellularly. Plasma chloride level rose as the negative chloride balance increased. The increase in the plasma chloride concentration must be due, not only to the reabsorption of this ion from the colon, but also to a greater loss of water and fixed base from the extracellular space than of chloride. A more gradual depletion of the extracellular chloride occurs over a forty-eight-hour period when the bromide space eventually decreases. At the end of forty-eight hours the losses of sodium and chloride, both in tube and voided excreta, are low, but potassium loss remains relatively high. The conservation of sodium at this time reflects a compensation by the animal secondary to the acidotic state. Thus the effects of dehydration are profound. Acidosis is enhanced and there is rapid loss of sodium and potassium. Such a situation may be compared to infant diarrhea, where, too, there is a rapid depletion of sodium and potassium because of frequent evacuations resulting in marked dehydration, electrolyte imbalance, acidosis, and shock.

Starvation: Two dogs refused to eat and died after three weeks due to starvation. Studies of the chemical constituents of blood were obtained at intervals, but balance studies were not made. These animals developed hyperchloremic acidosis within one week after operation, showing a rise in plasma chloride, fall in blood CO_2, and no change in plasma sodium. However, they differed from the four animals which recovered in that they refused all food although they took water in large quantities. This course was followed eventually by a depletion of chloride, sodium, and potassium. Plasma chloride reached its highest level in one week, and then fell steadily until the time of death. Sodium level of the plasma was maintained until acidosis fully developed, and then it fell steadily. Potassium concentrations followed a similar

course. At death these animals showed marked emaciation and dehydration, with normal kidneys and ureters. These animals depleted themselves by continuously losing electrolytes from their colon without any replacement. Thus, the acidosis led to anorexia which produced further electrolyte depletion which, in turn, enhanced the acidosis; and thus a vicious cycle was set up.

Mercuhydrin: Evidence has been presented that the diuretic action of Mercuhydrin brings about a greater loss of the chloride ion than of the sodium ion.[20] To test the possible therapeutic value of this observation, one animal was given 0.5 ml. of Mercuhydrin intravenously for three days. Both the fluid intake and output increased. The hematocrit increased slightly and the blood urea nitrogen rose moderately. Plasma sodium fell and the sodium deficit increased. Plasma chloride levels fell toward normal, the chloride output increased, and chloride balance became more negative. Concentrations of sodium, potassium, and chloride in tube excreta were slightly above voided concentrations, but the concentrations in both types of excreta were less than those obtained during the period of postoperative equilibrium. The diuresis that occurs presents a comparatively less concentrated electrolyte solution to the colon. The increased volume of fluid leads to increased and more rapid evacuation of the bowel with resulting loss of all electrolytes. Therefore, the conclusion is reached from this study that there is no therapeutic use of Mercuhydrin in the treatment of hyperchloremic acidosis. In fact, in view of the depletion of water and cations as well as anions, its use may be limited to patients receiving adequate fixed base and water, or might be best avoided since elimination of the excess chloride and acidosis can be corrected by simpler and safer ways.

SUMMARY AND CONCLUSIONS

These metabolic studies show that renal damage is not a sine qua non for the development of hyperchloremic acidosis following ureterosigmoidostomy. The acidosis is a consequence of differential intestinal absorption, which involves a balance of both fluid and electrolytes. The prevention or correction of acidosis will result from the proper intake of both water and fixed base, while rapid and severe deterioration may occur if these factors are not considered.

The electrolyte shifts attending the administration of the various substances and the changes attending dehydration corroborate this impression. When sodium bicarbonate is given there is a correction of the acidosis with the development of a negative chloride balance. When chloride ion is presented in excessive amounts, as during the periods of ammonium chloride administration, the situation was reversed, and acidosis and high serum chloride levels developed despite a negative chloride balance in the majority of instances.

Attempts to explore the mechanisms of the acidosis utilizing anion-exchange resins and glutamic acid were essentially inconclusive. Dehydration studies, however, with space measurements of the various body compartments were interesting because of the intensity and speed with which the changes

developed, emphasizing the necessity for continued large fluid intakes with proper electrolytes. The accelerated development of acidosis, with loss of sodium and potassium, is attended by marked contraction of the blood volume with a shocklike state developing.

These data would be of little significance unless the practical clinical application of such information is understood. Although poorly functioning kidneys are not necessary for the development of the syndrome, their presence enhances the likelihood of its development, and makes more difficult its correction. The important features to stress clinically in the management of these patients are (a) large fluid intake, up to 3,000 c.c. daily, (b) low to moderate chloride intake (40 to 100 meq.), (c) an excess of fixed base with anions which can be metabolized, such as bicarbonate, lactate, and citrate, and (d) frequent evacuation per rectum.

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PLASMA RETENTION AND URINARY EXCRETION OF DEXTRAN AND MODIFIED FLUID GELATIN IN COMBAT CASUALTIES

A Study in Korea

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LIMITATIONS in the availability of whole blood forward of the surgical hospital as well as the subsequent occurrence of homologous serum hepatitis following the administration of dried human plasma have repeatedly complicated the clinical management of the combat casualty. Following the successful use of dextran and modified fluid gelatin in experimental animals and in surgical patients,[8] these materials were made available to forward medical units during the Korean conflict for evaluation of their effectiveness as resuscitative and supportive agents. Further evaluation was necessary since the fate and the limitations of use of these compounds in severely injured patients had not been sufficiently investigated. In addition, the potential usefulness of such information in managing casualties of future disasters was obvious.

PURPOSE

To substantiate adequately the clinical observations on the effectiveness of dextran and gelatin in combat casualties,[1, 2] certain metabolic studies were necessary. It was believed that measurement of the circulatory retention of the plasma expander would be the best index of the degree and longevity of circulatory support. Measurement of urinary excretion rates would offer an index of the method of elimination as might be affected by marked circulatory, renal,[10] and metabolic disturbances accompanying massive trauma and hypotension. Of basic importance for the management of combat casualties was the relationship of effective circulatory support to evacuation time. During the period of this study (January, 1953, to August, 1953) the average evacuation time was approximately 3.5 hours, and these experiments were designed to evaluate the potential use of dextran and gelatin as the sole supportive agents during evacuation.

MATERIALS AND METHODS

Of the several hundred patients who received dextran or gelatin, sixteen of the seriously wounded dextran patients and ten of the seriously wounded

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gelatin patients were selected for this study. The dextran used was a product of the Commercial Solvents Corp., Lot 250 R2, having an average molecular weight of 42,000*; the modified fluid gelatin was a product of the Knox Gelatine Company, Inc., Lot MFG #9, having an average molecular weight of 34,000.†

All patients studied were young, male, United Nations combat casualties, sustaining injuries from artillery, mortar, grenade, land mine, or small arms fire. Some appeared in extremis upon admission, with imperceptible pulse and blood pressure. In general, they represent the type of casualty that required immediate blood replacement and extensive surgical treatment. Table I demonstrates the wound distribution in the patients studied.

TABLE I. DISTRIBUTION OF WOUNDS IN TWENTY-SIX COMBAT CASUALTIES USED FOR METABOLIC STUDIES OF DEXTRAN AND GELATIN

SITE OF PRIMARY INJURY	SITES OF ADDITIONAL INJURIES						
	CHEST	ABDOMEN	AMPUTATION	COMPOUND FRACTURE	MAJOR ARTERY	MASSIVE SOFT TISSUE	EXTREMITY PERFORATION
Chest	(1)*	0	0	1	0	1	1
Abdomen	0	(15)	2	8	3	9	8
Amputation	0	2	(5)	4	2	3	5
Compound fracture	1	8	4	(14)	2	8	11
Major artery	0	3	2	2	(4)	3	4
Massive soft tissue	1	9	3	8	3	(14)	14
Extremity perforation	1	8	5	11	4	14	(20)

*Figures in parentheses indicate total sustaining specific wound.

An attempt was made to follow a strict protocol, but in the majority of instances deviation from the protocol was necessitated by the patient's condition. Nevertheless, the unanticipated complications, although destroying certain uniformity, were invaluable in determining the effectiveness and role of these expanders in the treatment of severely wounded.

In general the procedure employed was as follows: Upon admission, all patients received immediate resuscitation, and operation was initiated only after blood volume replacement. Support of the circulation with whole blood continued during the operative procedure. Immediately after operation, a plasma volume determination was performed (T 1824), and the infusion of the plasma expander started. The time of the infusion varied, in accordance with the patient's condition. If possible, 1,000 c.c. was administered within three hours, as the standard dose. However, some patients received as much as 3,000 c.c., and the infusion time was as long as fourteen hours per 1,000 c.c. in one patient. The average infusion times per unit (500 c.c.) of dextran and gelatin were 2.7 hours and 2.5 hours, respectively. The immediate postoperative period was selected for these studies, since major hemorrhagic loss of the plasma expander could not be controlled prior to this time. Nevertheless, many of the patients were still hypotensive and in very serious condition at the time of the study.

*Molecular weight determination by Research Unit, Fort Totten, New Jersey.
†Molecular weight determination by University of Wisconsin.

During the entire period of infusion and for the length of the study, urine was collected from an indwelling catheter. Aliquots for chemical analysis were taken immediately after the infusion and if the volume was sufficient to permit accurate sampling, at three-, six-, twelve-, twenty-four-, forty-eight-, and seventy-two-hour intervals. Samples were collected from a few patients for periods up to seven days for each expander. Heparinized blood samples were drawn simultaneously, and additional plasma volumes determinations performed, if feasible, immediately postinfusion and at six-, twenty-four-, and seventy-two-hour intervals thereafter. Intermediate plasma volumes were determined by interpolation.

Chemical analyses were performed at the forward surgical hospital. Samples that were not analyzed immediately were stored in the frozen state until analysis was feasible. Plasma and urinary dextran levels were determined by the method of Bloom,[3] with only minor modification in technique necessitated by the situation. The procedure, in brief, consisted of alkaline hydrolysis of any protein, precipitation and isolation of macromolecular saccharides, and colorimetric determination of these saccharides with concentrated sulfuric acid and anthrone.

Gelatin determinations in plasma and urine were performed by the measurement of hydroxyproline resulting from acid hydrolysis of the sample, by the method of Neuman and Logan.[11] The method uses p-dimethylamino benzaldehyde for color development. The use of known quantities of gelatin for standards enabled conversion of hydroxyproline levels to gelatin levels. Plasma volume determinations were by a T 1824 dilution procedure, basically that of Gregersen,[7] using three interval measurements to assure complete mixing. Occasionally, mixing appeared incomplete after the third sampling. Such determinations were discarded and values estimated by interpolation or clinical judgment.

RESULTS

The data obtained from the sixteen patients receiving dextran and the ten receiving gelatin are reported on the scattergraphs shown in Figs. 1 through 4. Figs. 1 and 2 show the rate of disappearance from the plasma and Figs. 3 and 4 show the cumulative urinary excretion for dextran and gelatin, respectively. The scatter of the individual points is indicative of the variation. As Figs. 1 and 2 demonstrate, both expanders remained in the circulation for approximately the same period of time.

Six hours after complete infusion, an average of only 21 per cent and 23 per cent of dextran and gelatin, respectively, remained. Twelve hours postinfusion an average of only 15 per cent remained for each expander. Subsequent levels fell logarithmically with time to less than 3 per cent at seventy-two hours postinfusion. This rapid disappearance from the plasma is clearly a function of urinary excretion as indicated by Figs. 3 and 4. Six hours postinfusion, an average of 45 per cent and 60 per cent of the infused dextran and gelatin had been excreted in the urine. The amount recovered in the urine continued to reflect the plasma loss until at seventy-two hours, 58 per cent and 75 per cent

had been excreted. It should be noted that the difference in the total quantities excreted need not reflect a true difference in excretion of macromolecular weight compounds, since inherent differences in chemical methodology exist. The method employed for the dextran determinations will determine dextran and some of the polysaccharide intermediary metabolites thereof. However, the method employed for gelatin will detect not only the parent molecule but also the intermediary metabolites, even to the free amino acid stage. Thus, the additional amount of urinary gelatin may reflect the additional metabolic products detected by the chemical procedure. This same consideration should be applied to the interpretation of the different slopes of the linear portions of the urinary excretion curves, Figs. 3 and 4. The steeper slope of the delayed gelatin excretion curve is probably a reflection of the additional metabolites detected by the chemical procedure.

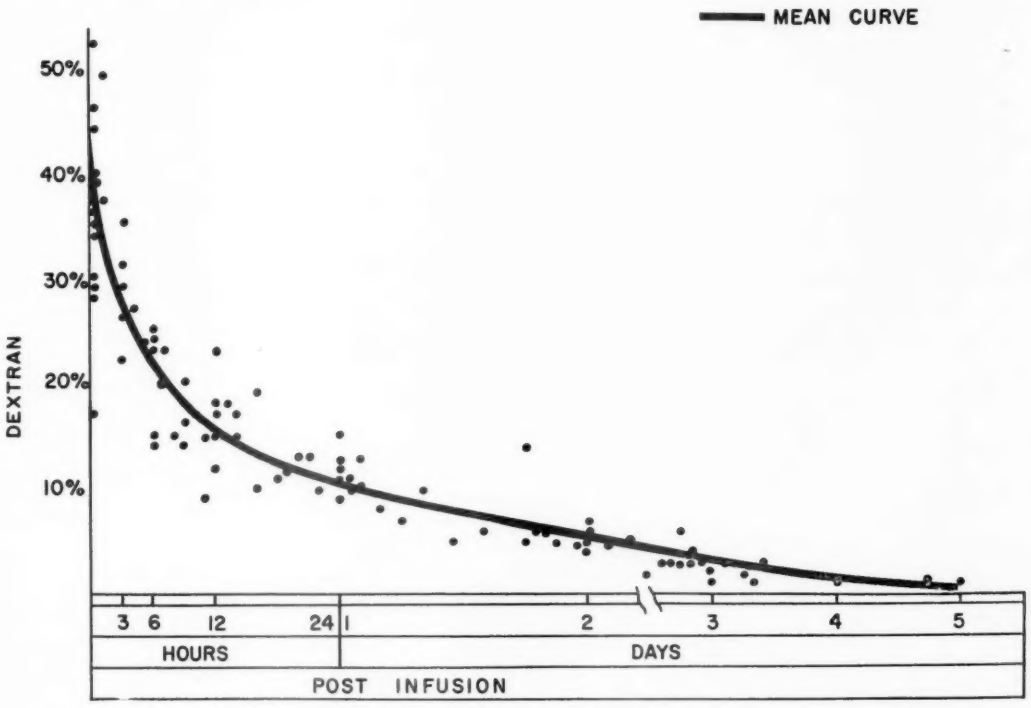

Fig. 1.—Percentage of infused dextran in plasma of sixteen combat casualties.

Addition of the cumulative excretion and plasma retention at any period of time reveals a significant quantity of either dextran or gelatin unaccounted for by these studies. Six hours postinfusion, this "unaccounted for" fraction averaged 34 per cent for dextran and 17 per cent for gelatin. Loss through hemorrhage into extravascular space, by metabolism,[5] storage, and by other excretory pathways[6] may all be factors contributing to this unaccounted for fraction. This difference in the quantity of unaccountable dextran and gelatin may reflect the difference in specificity of the analytical methods.

The cases heretofore reported have been studied following operation after hemorrhage was controlled. Of additional importance in evaluating the prac-

ticality of an expander in the treatment of mass casualities was information regarding circulatory retention prior to surgical therapy. Therefore, a series of ten casualties were administered dextran at a forward aid station and the plasma concentration measured between one and four hours later, upon arrival of the patient at a surgical hospital. These patients had no definitive treatment before arrival at the surgical hospital, only routine nonsurgical measures being employed to control hemorrhage.

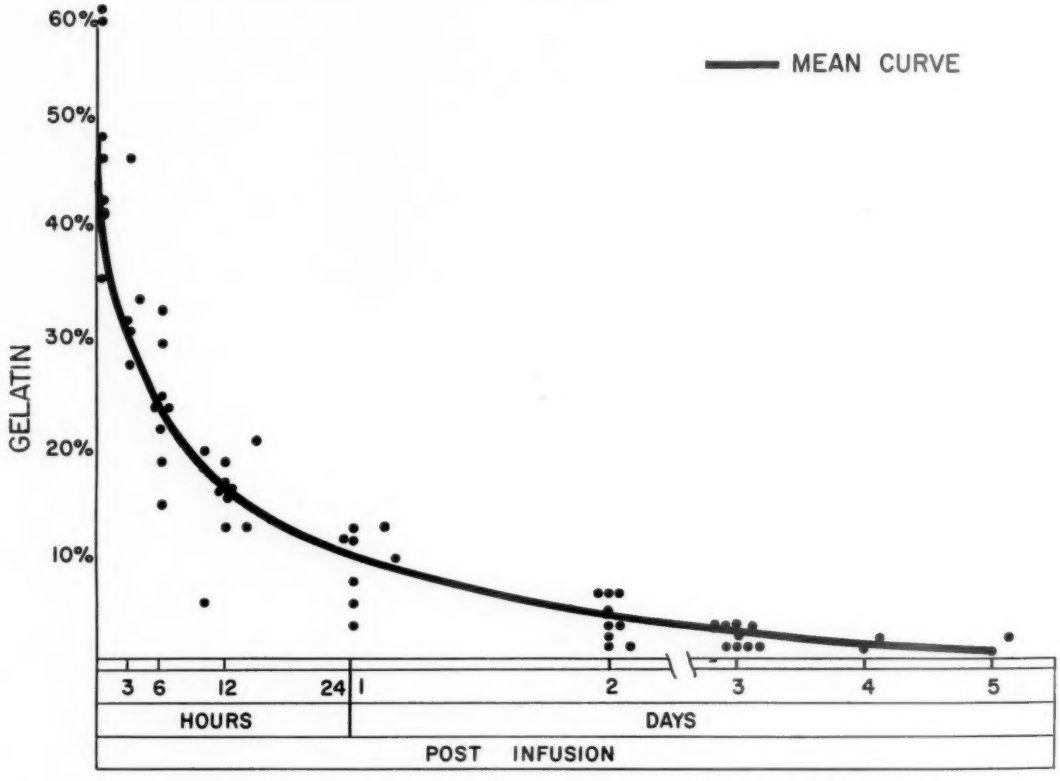

Fig. 2.—Percentage of infused gelatin in plasma of ten combat casualties.

Upon admission to the surgical hospital, the blood pressure was determined, and a blood sample drawn for chemical analysis. Blood volume determinations were impossible since hemorrhage was not adequately controlled and blood transfusions were needed almost immediately. For the purpose of calculating the percentage of the expander remaining in the circulation, it was necessary to make an estimation of plasma volume based upon clinical judgment, weight of the patients, and knowledge obtained from hundreds of T 1824 plasma volume determinations on other patients. The values used ranged from 2,200 to 2,500 c.c., depending upon these conditions. Table II shows the degree of hypotension upon admission to the surgical hospital and the approximate percentage of dextran remaining in the plasma at this time. It was observed that all ten patients arrived without serious hypotension although many were seriously wounded and required multiple whole blood transfusions before and during

operation. It was also observed that from 23 per cent to 42 per cent of the plasma expander remained in the plasma, depending in general upon the time required for evacuation. The rate of disappearance from the circulation appears somewhat greater than in postoperative patients. This difference, however, appears small enough to be explainable by the existing hemorrhage.

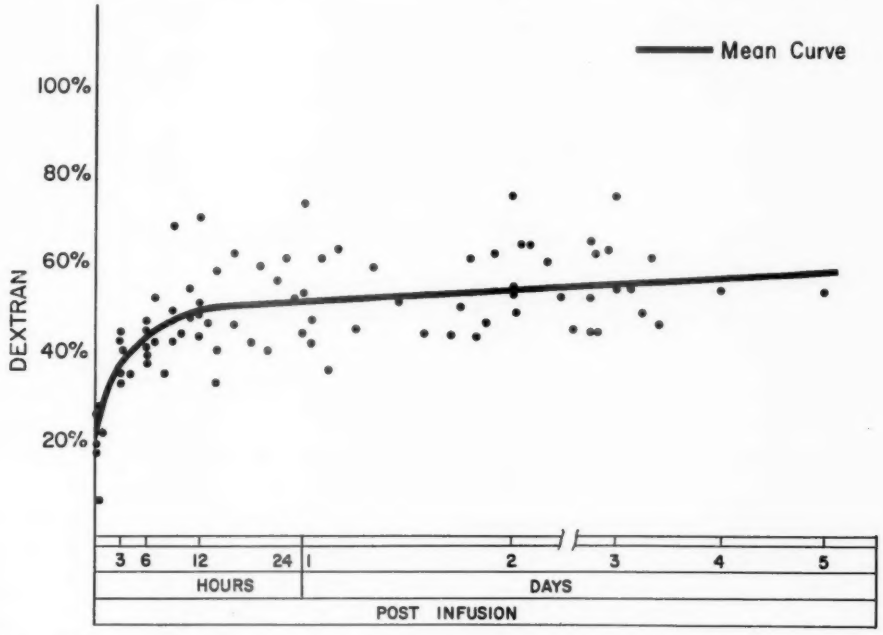

Fig. 3.—Cumulative percentage of dextran excreted in the urine of sixteen combat casualties.

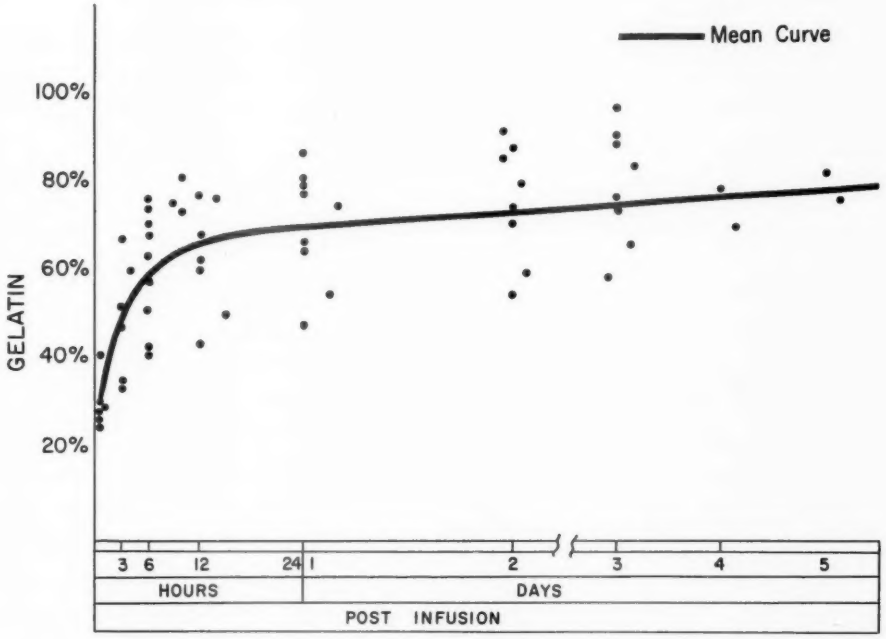

Fig. 4.—Cumulative percentage of gelatin excreted in the urine of ten combat casualties.

TABLE II. PLASMA RETENTION OF DEXTRAN DURING EVACUATION OF COMBAT CASUALTIES

TIME OF EVACUATION (HR.)	UNITS OF DEXTRAN ADMINISTERED	BLOOD PRESSURE AT END OF EVACUATION	APPROXIMATE % OF PLASMA DEXTRAN AT END OF EVACUATION
1	1	128/50	41
1	2	100/68	40
1.5	1	110/50	30
1.5	1.6	160/80	42
1.5	2	90/70	27
1.5	2	110/58	25
2	1	120/68	32
2	2	—	32
3.5	2	150/80	23
4	1	120/80	80

DISCUSSION

Previous investigators have demonstrated the relationship between circulatory retention and molecular size of dextran and gelatin.[4, 9] Therefore, any interpretation of the results of this study must take consideration of these facts. Because of the low molecular weight of both the dextran and gelatin used in this study, prolonged retention could not be anticipated. However, in order to decide if the disappearance rate was faster in the seriously wounded, it is necessary to compare results with a study in normal individuals, administered the expander with the same molecular distribution. Although such a study is not, to our knowledge, available for dextran, it is available for gelatin. Rousselot,[12] using the same lot of gelatin as employed in our other studies, found that the plasma retention of ten normal human beings averaged 35 per cent six hours postinfusion and 12 per cent twenty-four hours postinfusion. Since their infusion time was only twenty minutes as compared with our 2.5 hours per unit (a lag of approximately four hours for 2 units), our retention figures of 23 per cent at six hours and 9 per cent at twenty-four hours are quite comparable. We, therefore, feel that the circulatory retention of gelatin in seriously wounded combat casualties is not significantly different from that found in the normal person.

One of the basic limitations to the use of dextran and gelatin for the maintenance of blood volume is their temporary retention. Figs. 1 and 2 clearly emphasize this consideration. However, the circulatory retention of both dextran and gelatin was of sufficient duration to permit circulatory support during an evacuation period of several hours. It should be emphasized that the retention studies herein reported are based on rather slow drip infusions, averaging 2.5 hours per 500 c.c. Since the infusion of plasma expanders in practice often took place almost continuously during evacuation, the immediate postinfusion retention (approximately 40 per cent) was an index of the degree of expansion upon the arrival of the casualty at the surgical hospital. Successful management of the patient during evacuation was, therefore, possible despite the temporary volume expansion. More prolonged expansion would be desirable for situations involving greater delay before the administration of whole blood

and undoubtedly could be furnished by larger molecular fractions.[4, 9] However, the expansion obtained from 42,000 molecular weight dextran and 34,000 molecular weight gelatin was satisfactory for the short evacuation time in Korea.

CONCLUSION

Plasma retention and urinary excretion of dextran (average molecule size, 42,000) and modified fluid gelatin (average molecule size, 34,000) have been followed in a total of twenty-six seriously wounded combat casualties. No significant difference in plasma retention was observed between the two expanders. The retention of both was of short duration, 21 per cent or 23 per cent being retained in the plasma six hours postinfusion. This rate did not appear to be significantly different from that in normal human beings receiving the same molecular weight fraction (gelatin). The rapid loss of the expander from the plasma was reflected by a rapid urinary excretion. Nevertheless, both expanders, when administered slowly, maintained a circulating concentration capable of sufficient volume expansion to support many casualties for several hours before blood administration.

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SENSITIVITIES OF TEN SPECIES OF CLOSTRIDIA TO PENICILLIN, AUREOMYCIN, TERRAMYCIN, AND CHLORAMPHENICOL

A Study of Battle Wounds in Korea

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BATTLE casualties in the Korean conflict suffered less from wound infections than had casualties in any previous war or conflict. During the last half of the conflict, gas gangrene was a rarity and death from gas gangrene was almost unknown.[1] The success in preventing severe clostridial infections was probably due to the repair of arterial injuries, early and adequate débridement of wounds, and the early and consistent use of antibiotics. It was demonstrated in Korea,[2] as had been shown in earlier wars,[3, 4] that clostridia were present in approximately 46 per cent of wounds at the time of primary débridement. The average time lag after injury to reaching the forward surgical hospital was only 3.5 hours on the Eastern Front during the last eighteen months of the conflict, the subsequent time lag before reaching the operating room being only 1 to 1.5 hours.

Thus in the latter half of the conflict, short evacuation times and small casualty loads permitted optimal surgical care and resulted in a low incidence of severe clostridial infections.

Mass casualties such as occurred at times in Korea, in earlier wars, or which might occur with atomic warfare and civilian disasters would not permit the early or individualized attention given the soldiers during the period of this study. For these reasons, as well as the possibility of improving somewhat the care of the soldier in Korea, a re-evaluation of the antibiotic program in the combat zone was undertaken. Throughout the latter part of the conflict, penicillin (300,000 to 600,000 units) was administered intramuscularly as the casualty reached the battalion aide station. Following the subsequent operation, casualties routinely received penicillin (300,000 units) every twelve hours. In addition, casualties with intraperitoneal injuries, arterial injuries, or intrathoracic injuries received 0.5 Gm. of streptomycin every twelve hours. Aureomycin was available but was used infrequently.

MATERIAL AND METHODS

In a previous study, eleven wounds inflicted during the Korean conflict were examined bacteriologically throughout the first week of healing.[5] This

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was done by culture of tissue excised from the open wound at the time of primary débridement and every two days thereafter during the ensuing week. Fifty-six clostridial isolates and numerous aerobic organisms were obtained. In this study the sensitivities of the clostridial isolates to penicillin, Aureomycin, Terramycin, and chloramphenicol are presented and correlated with human serum levels of these antibiotics.[6-8]

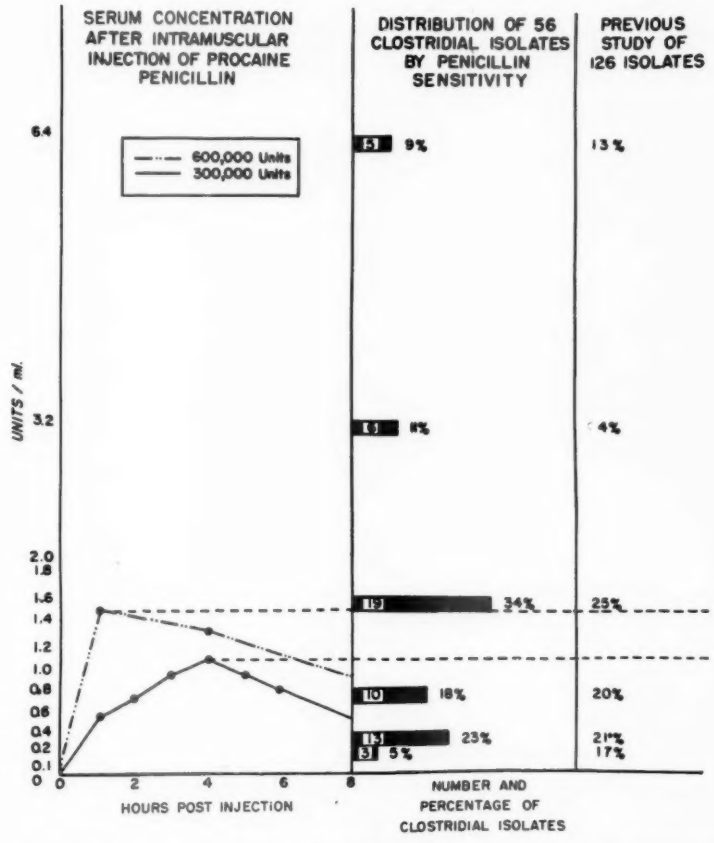

Fig. 1.—Sensitivity of the clostridial flora to penicillin. The percentages in the column on the far right are the results of an earlier study of battle wounds at the time of primary débridement.[2] The dotted line represents the maximal concentrations of the drug.

Isolates were grown for eighteen hours at 37° C. in tubes of Brewer's thioglycollate broth. One milliliter of this culture was transferred to a flask containing 100 ml. of thioglycollate broth. This mixture served as seed broth. The antibiotics were prepared in thioglycollate broth so that the mixture of 2 ml. of the antibiotic solutions and 2 ml. of the seed broth gave the following final concentrations of antibiotics in units per milliliter or micrograms per milliliter:

Penicillin 0.025, 0.05, 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 6.4 units per milliliter.
Aureomycin 0.0125, 0.025, 0.05, 0.1, 0.2, 0.4, 0.8, 1.2, 1.8, 3.2 μg per milliliter.
Terramycin 0.025, 0.05, 0.1, 0.2, 0.4, 0.8, 1.2, 1.6, 3.2, 6.4 μg per milliliter.
Chloramphenicol 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 32 μg per milliliter.

TABLE I. DISTRIBUTION OF SENSITIVITIES OF CLOSTRIDIAL ISOLATES TO FOUR ANTIBIOTICS

SPECIES	TOTAL NO.	PENICILLIN UNITS/ML.						AUREOMYCIN μG/ML.						TERRAMYCIN μG/ML.						CHLORAMPHENICOL μG/ML.								
		0.2	0.4	0.8	1.6	3.2	6.4	0.0125	0.025	0.05	0.1	0.2	0.8	0.05	0.1	0.2	0.4	0.8	3.2	1	2	4	6	8	12	16	20	32
Clostridium bifermentans	17		2	2	10	3		1	2	12	2			1	11	3		2		2	4	5	3			3		
Clostridium butyricum	1					1				1					1							1						
Clostridium lentoputrescens	1	1							1					1						1								
Clostridium novyi	8		2	2	1	1	2			2	3	3			1	4	2	1				4	1	1	1		1	
Clostridium paraputrificum	2				2						1		1		1				1				2					
Clostridium perfringens	7	1	2	2	2				1	1	3	2		1	1	1	3	1				1	2	2		2		
Clostridium sordellii	2			1	1					1	1			1		1							1					1
Clostridium sporogenes	11	1	3	2	2	1	2			3	7	1		1	6	2	1	1				1	3		3	2	1	1
Clostridium tetanomorphum	2		1	1						1	1			1			1					1	1				
Clostridium unclassified	5		3		1		1			4		1		1	3	1					1	2	1			1		
Total	56	3	13	10	19	6	5	1	4	25	18	7	1	7	24	12	7	5	1	3	5	15	14	3	4	7	3	2

The tubes were incubated at 37° C. for twenty hours. At this time the tube of lowest concentration showing no visible growth was read as containing the concentration of antibiotic which caused complete inhibitions of growth. A control tube containing 2 ml. of seed broth and 2 ml. of thioglycollate broth was used for each organism tested and incubated under the same conditions.

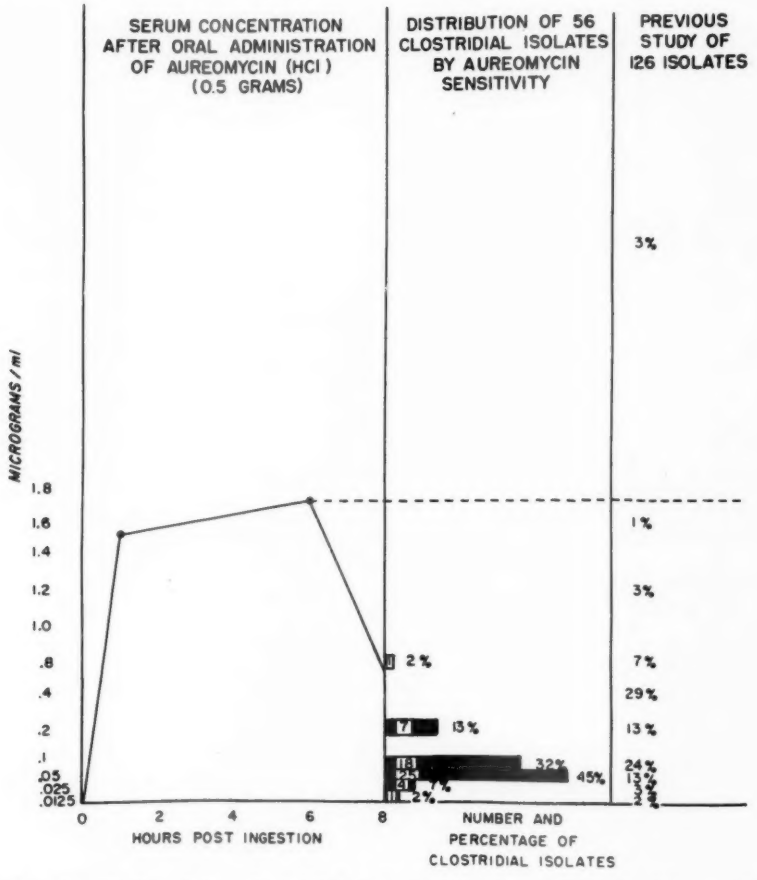

Fig. 2.—Sensitivity of the clostridial flora to Aureomycin. This figure, constructed as was Fig. 1, shows that in the current study all fifty-six clostridial isolates were inhibited by the therapeutic concentration of Aureomycin.

Table I shows that sensitivities of the fifty-six clostridial isolates to the antibiotics penicillin, Aureomycin, Terramycin, and chloramphenicol follow normal distribution curves. The range of inhibition for penicillin is 0.2 to 6.4 units per milliliter, for Aureomycin 0.0125 to 0.8 μg per milliliter, for Terramycin 0.05 to 3.2 μg per milliliter, and for chloramphenicol 1.0 to 32.0 μg per milliliter. Those dilutions which did not inhibit are omitted.

Fig. 1 shows human serum concentrations following the administration of 300,000 and 600,000 units of procaine penicillin (G)[6] and correlates these levels with the number of clostridial isolates inhibited by increasing concentrations of penicillin. A comparison of serum levels in Fig. 1 with concentrations of penicillin necessary for inhibition demonstrates that approximately

80 per cent of the clostridial isolates are inhibited by the highest serum level reached after the administration of 600,000 units. Since this high level is maintained for a short period only, the percentage of organisms falling outside the range of inhibition would probably become greater when the entire absorption curve is considered.

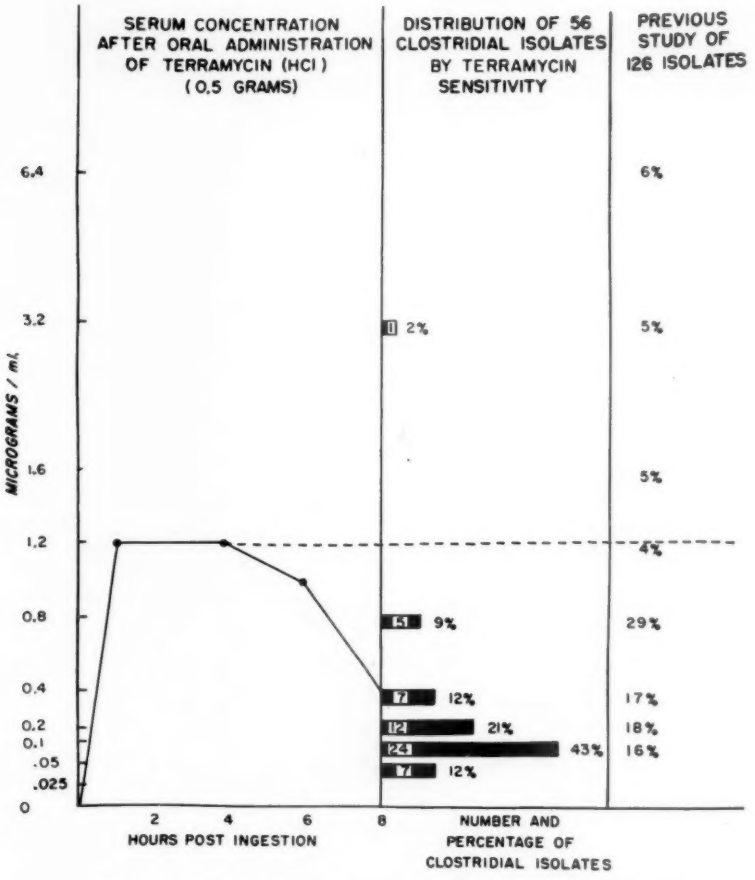

Fig. 3.—Sensitivity of the clostridial flora to Terramycin.

Following the administration of 300,000 units, 46 per cent of the organisms would, as indicated by the in vitro assay, be inhibited by the maximal concentration found in the serum. The sensitivities in this study correspond closely with the results of a previous study of 126 clostridial isolates from many battle wounds at the time of initial débridement.[2] According to the previous study, 83 per cent and 58 per cent, respectively, would be inhibited by the maximal serum concentration following the two dosages (Table II).

Following the oral administration of 0.5 Gm. of Aureomycin, the serum concentration ranges between 1.5 and 1.7 μg per milliliter for six hours[7] (Fig. 2). This concentration proved inhibitory, in vitro, to 100 per cent of the fifty-six clostridial isolates in this study and 97 per cent of the 126 isolates in the earlier study.

Following the oral administration of 0.5 Gm. of Terramycin, the serum concentration ranges around 1.2 μg per milliliter between one and four hours after ingestion[7] (Fig. 3). As indicated by the in vitro studies, this concentration was inhibitory to 98 per cent of the fifty-six clostridial isolates in this study and 84 per cent of the 126 clostridial isolates studied previously.

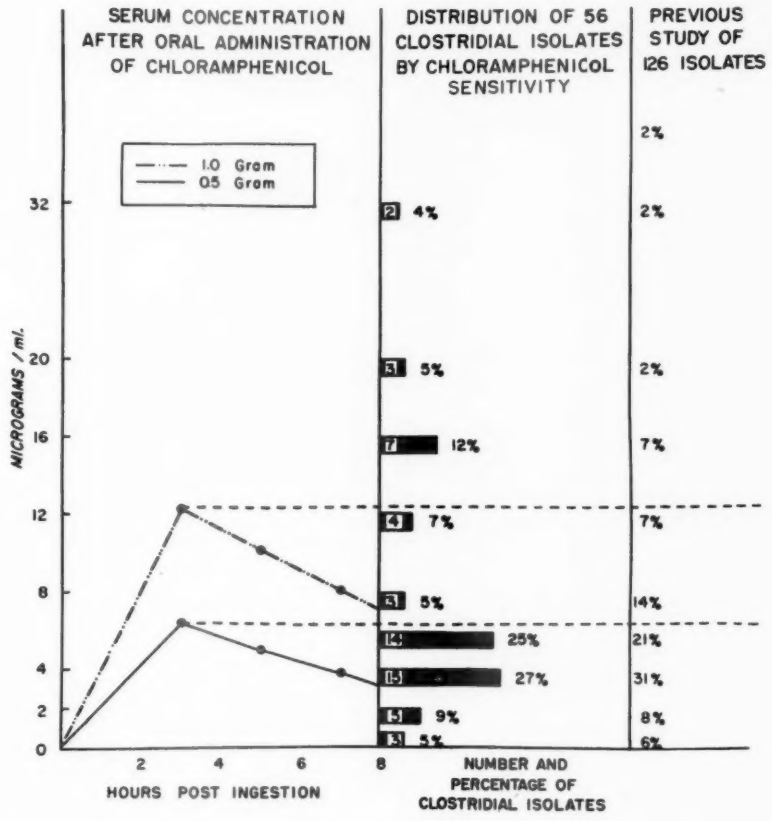

Fig. 4.—Sensitivity of the clostridial flora to chloramphenicol (Chloromycetin).

Following the oral administration of 0.5 Gm. of chloramphenicol (Chloromycetin), the serum concentration rises to 6 μg per milliliter after three hours.[8] The concentration then gradually decreases. This maximal concentration, in vitro, inhibited the growth of 66 per cent of the fifty-six isolates in this study, a finding which confirms the earlier study. After the administration of 1.0 Gm. of chloramphenicol, the serum concentration rises to 12 μg per milliliter, a concentration sufficient to inhibit, in vitro, 78 per cent of the organisms in the current study and 87 per cent in the earlier studies.

DISCUSSION

Antibiotic therapy has not, and probably never will, supplant débridement in the fundamental role of preventing or treating infections of war wounds.

As an adjunct to débridement, all four of the antibiotics included in this study, however, appear to be beneficial in preventing or minimizing clostridial infections.[9-15]

TABLE II

DRUG	DOSAGE	PER CENT OF CLOSTRIDIAL ISOLATES INHIBITED BY MAXIMAL (SERUM) CONCENTRATION	
		56 ISOLATES OF CURRENT STUDY	126 ISOLATES OF PREVIOUS STUDY
Procaine penicillin	300,000 units	46	58
Procaine penicillin	600,000 units	80	83
Aureomycin	0.5 Gm.	100	97
Terramycin	0.5 Gm.	98	84
Chloramphenicol	0.5 Gm.	66	66
Chloramphenicol	1.0 Gm.	78	87

Of the drugs and dosages studied, and within the limitations of the in vitro sensitivity method, Aureomycin or Terramycin would appear to be the drugs of choice in preventing or treating clostridial wound infections.

Experimental studies conducted in this laboratory have shown that the concentrations of most antibiotics in the muscle are less than concentrations found in the serum.[16] If the time should ever come again when, as a compromise, antibiotic therapy must be used as a bulwark to support delayed surgery of mass casualties, increased dosages of these drugs might be in order. Under such circumstances, the advantages of drugs which are effective after oral administration are self-evident.

CONCLUSIONS

In vitro sensitivity studies of the flora of the Korean battle wounds suggest that Aureomycin and Terramycin are more effective than penicillin and chloramphenicol in inhibiting the growth of clostridia.

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THE BACTERIAL FLORA OF HEALING WOUNDS

A Study of the Korean Battle Casualty

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SEVERAL studies have described the bacterial flora of battle wounds at the time of initial débridement. In one study during World War I, Stoddard[1] found *Clostridium perfringens* present in 80 per cent of wounds. MacLennan,[2, 3] working in the Middle East and later in Tripolitania and Tunisia during World War II, found that between 45 per cent and 50 per cent of the wounds contained clostridia, and commented that their absence from war wounds was "a matter of surprise rather than satisfaction, their presence for resignation rather than alarm." Neel and Cole[4] found in the Pacific area that 48 per cent of 160 wounds, cultured early after injury, contained clostridia. Except for differences in species distribution, the pattern of simple contamination was similar in wounds of the Korean casualties,[5] 46 per cent of which were found, at the time of primary débridement, to contain clostridia.

This study was undertaken to explore the fate of microorganisms in the open, débrided wound during the earlier stages of healing.

MATERIAL AND METHODS

Patients received their earliest surgical treatment at hospitals located within ten miles of the main line of resistance.

At battalion aide stations, external hemorrhage was controlled, the wounds were dressed, fluid replacement therapy begun, and tetanus toxoid and penicillin (300,000 to 600,000 units) were given routinely. The most seriously wounded patients were transported directly by helicopter to the surgical hospital. Less seriously wounded men were evacuated by ambulance and rechecked at collecting company and clearing company levels along the routes of evacuation.

When resuscitation was considered optimum, the patient was anesthetized and the wound field was cleansed with tincture of green soap and sterile water. The surrounding skin was prepared with tincture of Merthiolate and the surgical field was draped with sterile towels.

During March and April of 1953, eleven patients were selected for study. Selection was based on the accessibility of the wound for serial biopsies and on its location distant from any focus of subsequent contamination. In the

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majority of patients, the wound of entrance in the skin was small compared to the extent of destruction of the underlying subcutaneous tissue and muscle. Thus when a perforating wound was incised, a large cavity was sometimes found in the deeper layers.

The primary surgery of these wounds consisted of débridement of skin, subcutaneous tissue, and muscle. The wounds were then covered with fine mesh gauze and a thick sterile dressing. Each patient was given penicillin, 300,000 units, and streptomycin, 0.5 Gm., intramuscularly every twelve hours.

At the beginning of débridement, tissue blocks were taken from healthy muscle in the base of each wound. In addition, blocks of devitalized muscle were taken from six of the wounds. Subsequently, tissue blocks from typical areas of healing muscle were taken at two-day intervals during the ensuing week. For these secondary biopsies, the patients were returned to the operating room where sterile technique was used. After the last tissue block was taken and wound closure accomplished, patients were held one to three days and evacuated.

Each tissue block was placed in a medium of modified Robertson's cooked meat broth, the tube sealed with vaspar and shipped via air to the 406th Medical General Laboratory in Tokyo. Twenty control specimens, held and shipped in a similar manner, maintained viable organisms.

Isolation and Identification.—The incoming specimens were then incubated for twenty-four hours at 37° C.; at this time, 1 ml. was transferred to thioglycollate broth, which, in turn, was incubated for an additional eighteen hours at 37° C. A yeast extract blood agar plate and a chloral-hydrate sodium azide plate were streaked with a 4 ml. loop from the thioglycollate subculture and incubated anaerobically for forty hours. A representative of each morphologic colony was picked from each plate to thioglycollate broth. After an eighteen-hour incubation period, gram stains were made. The gram-positive, spore-forming bacilli were plated on blood agar base and incubated aerobically. Those that showed no growth on the aerobic plates were replated on blood agar base and incubated anaerobically for forty-eight hours to determine the uniformity of colonial type. A representative colony was picked to thioglycollate broth to be used as a seed culture for biochemical identification.

Identification of the aerobic flora was effected by standard laboratory techniques. The clostridia were identified by using a modification of the Reed and Orr classification,[6] utilizing ten carbohydrates, hydrogen sulfide production, litmus milk reaction, gelatin liquefaction, indole production, acrolein production, nitrate reduction, and pathogenicity for guinea pigs.

RESULTS

Anaerobes.—Nine of the eleven wounds studied contained one or more species of clostridia at the time of débridement (Table I). One wound (Patient No. 1) did not demonstrate clostridia on initial culture but showed one species on the fifth day. Clostridia were never isolated from the remaining wound (Patient No. 10). Two of the wounds (Patients Nos. 3, 7) were clinically

TABLE I. THE BACTERIAL FLORA OF ELEVEN WOUNDS DURING THE FIRST WEEK OF HEALING

PATIENT	TIME LAG WOUNDING TO SURGERY (HR.)	ANTIBIOTIC AND TIME GIVEN PRIOR TO SURGERY	WOUNDING AGENT	ANAEROBES	AEROBES	ANAEROBES	AEROBES	ANAEROBES	AEROBES	ANAEROBES	AEROBES
				1st Hospital Day		3rd Hospital Day		5th Hospital Day		7th Hospital Day	
1	4	300,000 units penicillin, 3½ hr.	Small arms	None isolated	Streptococcus beta Corynebacterium Staphylococcus H+S+M–C–* Staphylococcus H+S+M+C+	None isolated	Streptococcus beta Streptococcus alpha Bacillus species	*Cl. novyi*	*Pseudomonas aeruginosa* Paracolon species Streptococcus alpha Bacillus species	Not examined	
				1st Hospital Day		3rd Hospital Day		5th Hospital Day		7th Hospital Day	
2	9	300,000 units penicillin, 7½ hr.	Shell fragments	*Cl. novyi*	Streptococcus nonhemolytic– Bacillus species	None isolated	Streptococcus beta	None isolated	Corynebacterium Streptococcus beta Staphylococcus H+S+M+C+	None isolated	Streptococcus beta *Escherichia coli*

PATIENT	TIME LAG WOUNDING TO SURGERY (HR.)	ANTIBIOTIC AND TIME GIVEN PRIOR TO SURGERY	WOUNDING AGENT	ANAEROBES	AEROBES	ANAEROBES	AEROBES	ANAEROBES	AEROBES	AN-AEROBES	AEROBES	AN-AEROBES	AEROBES
				1st Hospital Day		3rd Hospital Day		5th Hospital Day		6th Hospital Day		8th Hospital Day	
3	6	300,000 units penicillin, 5 hr.	Small fragment	*Cl. perfringens* *Cl. bifermentans* *Cl. paraputrificum*	Streptococcus beta Streptococcus nonhemolytic *Sarcina lutea*	*Cl. novyi* *Cl. perfringens* *Cl. sporogenes*	Streptococcus beta Streptococcus nonhemolytic Bacillus species *E. coli* Streptococcus alpha	*Cl. sporogenes* *Cl. bifermentans*	Streptococcus nonhemolytic Streptococcus alpha Bacillus species	*Cl. perfringens*	Streptococcus nonhemolytic Streptococcus alpha	*Cl. novyi* *Cl. sporogenes*	Streptococcus nonhemolytic
				1st Hospital Day		3rd Hospital Day		5th Hospital Day		7th Hospital Day		8th Hospital Day	
4	2	600,000 units penicillin, 2½ hr.	Small fragment	***Devitalized muscle:*** *Cl. bifermentans* *Cl. novyi* *Cl. multimentans* *Cl. sporogenes* *Cl. parabotulinum* ***Muscle after débridement:*** *Cl. tetanomorphum* *Cl. sporogenes*	Streptococcus nonhemolytic Streptococcus nonhemolytic Bacillus species Staphylococcus	*Cl. sporogenes* *Cl. bifermentans*	None isolated	*Cl. sporogenes* *Cl. bifermentans* *Cl. multifermentans* *Cl. butyricum* *Cl. carnis*	Bacillus species	*Cl. novyi*	Staphylococcus H+S+ M+C– Streptococcus nonhemolytic Bacillus species	**Not examined**	

TABLE I—CONT'D

PATIENT	TIME LAG WOUNDING TO SURGERY (HR.)	ANTIBIOTIC AND TIME GIVEN PRIOR TO SURGERY	WOUNDING AGENT	ANAEROBES	AEROBES	ANAEROBES	AEROBES	ANAEROBES	AEROBES	ANAEROBES	AEROBES
				1st Hospital Day		3rd Hospital Day		6th Hospital Day		8th Hospital Day	
5	10	No record	Mortar fragments	*Devitalized muscle:* *Cl. perfringens*	Streptococcus nonhemolytic Bacillus species	None isolated	Streptococcus beta Streptococcus nonhemolytic Bacillus species Staphylococcus H+S+M+C–	None isolated	Bacillus species	None isolated	Staphylococcus H+S+M+C–
				Muscle after débridement: None isolated	Streptococcus beta Streptococcus nonhemolytic Staphylococcus H+S+M+C– Bacillus species						
				1st Hospital Day		3rd Hospital Day		6th Hospital Day		8th Hospital Day	
6	6	300,000 units penicillin, 4 hr.	Shell fragments	*Devitalized muscle:* *Cl. tetani* *Cl. sporogenes* *Cl. novyi* *Cl. paraputrificum* *Cl. tetanomorphum*	Streptococcus nonhemolytic Streptococcus alpha Corynebacterium	None isolated	Bacillus species	None isolated	Bacillus species	None isolated	Streptococcus nonhemolytic *Ps. aeruginosa*
				Muscle after débridement: *Cl. butyricum*	Streptococcus beta Staphylococcus H+ Bacillus species						

				1st Hospital Day		3rd Hospital Day		6th Hospital Day		8th Hospital Day	
7	6½	300,000 units penicillin, 3½ hr.	Shell fragment wounds	*Cl. perfringens* *Cl. sordelli* *Cl. butyricum* *Cl. bifermentans*	Streptococcus nonhemolytic Bacillus species	*Cl. sordelli*	*Aerobacter aerogenes*	*Cl. perfringens* *Cl. bifermentans* *Cl. aerofoetidum* *Cl. butyricum*	*E. coli*	None	Streptococcus beta hemolytic Bacillus species *Serratia marcescens*

				1st Hospital Day		3rd Hospital Day		5th Hospital Day		7th Hospital Day	
8	6	300,000 units penicillin, 5 hr.	Land mine	*Devitalized muscle:* *Cl. paraputrificum*	Staphylococcus H+S+M–C– Bacillus species Paracolon species	None isolated	Streptococcus beta Streptococcus nonhemolytic Staphylococcus H–S+M+C–	None isolated	Streptococcus beta Staphylococcus H+S–M–C– Bacillus species Streptococcus nonhemolytic	None isolated	Streptococcus beta Staphylococcus H+S+M+C–
				Muscle after débridement: None	Streptococcus beta Staphylococcus nonhemolytic Staphylococcus H–S+M+C–						

				1st Hospital Day		4th Hospital Day	6th Hospital Day		8th Hospital Day	
9	6	300,000 units penicillin, 5½ hr.	Hand grenade	*Cl. carnis* *Cl. butyricum*	Bacillus species Streptococcus nonhemolytic	None isolated	None isolated	Bacillus species	None isolated	Staphylococcus H+S+M–C– Bacillus species Staphylococcus H+S+M+C+ Staphylococcus H–S+M+C+

TABLE I—CONT'D

				1st Hospital Day		4th Hospital Day		6th Hospital Day		9th Hospital Day	
10	4	No record	Shell fragments	*Devitalized muscle:* None isolated	Bacillus species Staphylococcus H+S+M+C+	None isolated	Bacillus species Streptococcus nonhemolytic	None isolated	Staphylococcus H+S+M+C–	None isolated	Staphylococcus H+S+M+C– Bacillus species Streptococcus nonhemolytic
				Muscle after débridement: None isolated	None isolated						
				1st Hospital Day		3rd Hospital Day		5th Hospital Day		7th Hospital Day	
11	3	300,000 units penicillin, 2½ hr.	Mortar fragments	*Devitalized muscle:* *Cl. sporogenes* *Cl. lentoputrescens*	Streptococcus beta Bacillus species Streptococcus nonhemolytic	None isolated	Streptococcus alpha Streptococcus nonhemolytic Bacillus species Corynebacterium species	None isolated	None isolated	None isolated	Bacillus species
				Muscle after débridement: None isolated	Staphylococcus H+S+M–C–						

*H+ = hemolytic.
H– = nonhemolytic.
S+ = salt resistant.
S– = salt susceptible.
M+ = mannite fermenting.
M– = mannite nonfermenting.
C+ = coagulase positive.
C– = coagulase negative.

infected but neither showed gas gangrene. Clostridia were absent from two-thirds of the wounds when studied after the initial surgery.

Aerobes.—All wounds contained a rich flora of gram-positive and gram-negative aerobes on initial culture (Table I). Without exception, these organisms persisted in the wounds during the first week of healing. There appeared, however, to be considerable variation in the number of organisms and species from one culture to the next.

Pathogenicities of Clostridia.—The following species of clostridia were found to be pathogenic in this laboratory by using the standard guinea pig inoculating procedure: *Clostridium perfringens, Clostridium fallax, Clostridium carnis, Clostridium novyi, Clostridium sordellii, Clostridium histolyticum, Clostridium difficile, Clostridium tetani,* and *Clostridium parabotulinum.*

The findings in this study compare favorably with pathogenicities of clostridia described previously.[7]

DISCUSSION

Although this series is small, the consistency of the observations permits certain conclusions to be considered. The rich aerobic and anaerobic flora demonstrated in most wounds confirmed the results of similar studies since World War I.

The absence of clostridia in two-thirds of cultures taken subsequent to the initial surgery suggests that the present methods of more complete débridement of devitalized tissue are important factors in reducing the bacterial population.

The two wounds (Patients Nos. 3, 7) in which adequate débridement was not carried out showed clinical evidence of infection and contained a rich clostridial and aerobic flora throughout the first week of healing. These findings are consistent with the belief that nonviable tissue is one of the necessary requirements for maintaining clostridia. The persistently rich aerobic flora in all cultures is not surprising since these organisms are widely found in skin, air, soil, and respiratory tract of the medical personnel.

The changing character of both the aerobic and the clostridial flora from one hospital day to another was observed in all wounds. Further contamination at wound dressing could account for the appearance of many new aerobic organisms. Antibiotic therapy may have influenced both the aerobic and the anaerobic flora, but it did not appreciably influence the flora in the presence of necrotic tissue. Culturing a single small tissue block from a large wound probably did not give a complete picture of the total bacterial population, but the consistency of the findings suggests that it provided a representative index of the bacterial flora.

Histologic studies of the same wounds are to be reported later; suffice it to say here that the bacterial flora, in the absence of necrotic tissue, did not appear to affect the healing of the open wound. Similarly, observation of hundreds of casualties demonstrated that the clean, contaminated wounds, when secondarily closed, healed satisfactorily.

CONCLUSIONS

1. Pathogenic and nonpathogenic clostridia were isolated in nine of eleven wounds at the time of initial surgery. All wounds contained a rich aerobic flora.

2. Only three of the nine wounds showing clostridia at the time of initial surgery contained these organisms in subsequent cultures. This would appear to indicate that the present methods of débridement and irrigation are effective in reducing the bacterial population in wounds.

3. At the time of secondary closure, pathogenic aerobic organisms are often present in the wound, but in the absence of other deterrents do not appear clinically to interfere with wound healing.

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PAPILLARY LYMPH NODULE HYPERPLASIA OF THE DUODENUM

(Report of a Case)

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LYMPH nodule hyperplasia of the rectum, appendix, colon, ileum, and stomach has been reported, but apparently no case of duodenal involvement has appeared in the literature. This paper presents a proved case of papillary lymph nodule hyperplasia of the first portion of the duodenum. It is important to stress the fact that this condition is easily recognized by its unique roentgenographic features and thus can be clinically differentiated from other diseases of the duodenum.

CASE REPORT

The patient (R.D. #X16404) was a 59-year-old white man who was admitted to Maimonides Hospital of Brooklyn on May 5, 1953, with a complaint of hemoptysis of three days' duration. In spite of the fact that the patient was known to have had severe hypertension for seven years prior to admission, he had enjoyed good health and was able to work steadily as a longshoreman until he was injured in an automobile accident two weeks prior to admission. At that time he was treated in another hospital for a period of ten days for contusions of the right chest, left mandible, and left leg. On May 2, 1953, the patient was seized with a violent spell of coughing while at home; whereupon he developed severe hemoptysis and was admitted to the hospital.

At the time of admission the patient's temperature was 99.8° F., pulse was 88 and regular, the blood pressure was 240/110. Examination of the lungs revealed no unusual findings. Auscultation of the heart revealed no abnormalities. The remainder of the examination was negative except for the presence of a reducible right femoral hernia.

Laboratory Data.—Blood count: Hemoglobin was 10.9 Gm., red blood cells 3,100,000, white blood cells 8,100, polymorphs 69, lymphocytes 20, monocytes 10, basophil 1; toxic granulations were present. Bleeding time was 5 minutes; clot retraction time 3 minutes, 30 seconds; prothrombin time 14. Platelets were 187,250. Blood serology was negative. Blood chemistry: Glucose was 95, urea nitrogen 37, creatinine 1.6. Urinalysis: Specific gravity was 1020, essentially normal except for occasional white blood cells, occasional hyaline casts, and occasional epithelial cells. The electrocardiogram showed signs compatible with left ventricular hypertrophy or with residual anteroseptal wall infarction. X-ray film of the lungs showed intensified parahilar markings bilaterally, but was otherwise normal. The examination of the sputum for acid-fast bacilli was negative.

On the day following admission the hemoptysis ceased. On the fourth hospital day the patient vomited a quantity of bright red blood and passed a large tarry stool. The following day all signs of gastrointestinal bleeding had disappeared. The patient received 1,000 c.c. of blood by indirect transfusion to restore his blood volume. Three days later a barium enema was done and found to be normal. A gastrointestinal series was normal except for the duodenal bulb, which revealed a smooth regular contour with a peculiar mucosal pattern of numerous shotlike filling defects which were thought to be due to intramural papillary excrescences. The diagnostic impression was a possible intramural tumor of the first part of

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the duodenum. The subsequent course of the hospitalization was uneventful, and there were no recurrences of hemorrhages. The tumor in the duodenum was deemed to be benign, and since the patient was thought to have a possible anterior wall myocardial infarction, he was discharged from the hospital on May 24, 1953, to convalesce from the pulmonary and gastrointestinal hemorrhages and to improve the cardiac status.

During the ensuing two months repeated cardiologic consultations revealed no changes in the electrocardiogram, and the cardiologist interpreted the condition as representing a possible old myocardial infarction or merely a case of left ventricular hypertrophy. Another gastrointestinal series revealed that the findings in the duodenum had not changed. Meanwhile, the patient developed repeated attacks of incarceration of the right femoral hernia. Since the cardiologist saw no contraindication to surgery, the patient was readmitted to Maimonides Hospital on Aug. 10, 1953, for a right femoral hernioplasty. Examination at this time revealed the same findings as noted on the previous admission. A right femoral hernioplasty was performed through the inguinal canal. On the third postoperative day the patient was walking about the corridor after eating a hearty breakfast when he suddenly slumped to the floor and expired shortly thereafter.

Fig. 1.—Gastrointestinal series showing shotlike filling defects in the duodenal bulb due to papillary excrescences of lymph nodule hyperplasia.

Autopsy Report (#A-119-53).—The autopsy was limited to examination of the viscera of the thorax and abdomen.

The thyroid was normal. The lungs were normal except for some areas of atelectasis. There was no evidence of pulmonary edema. No pulmonary emboli were found. The heart was markedly enlarged, with prominence of the left ventricle. It was seen, on opening into the endocardial cavity, that the left ventricle was markedly dilated while the right ventricle

was normal in size. The right ventricle measured 0.6 cm. in thickness and the left 1.8 cm. The valves were normal with the exception of the aortic valve, which showed marked calcification with stenosis and a lack of fusion of the cusps. The myocardium was beefy red in color and doughy in consistency. In the posterior wall of the left ventricle a pearly gray area was present which represented the site of a previous myocardial infarction. The right coronary artery was obliterated by an old organized thrombus at a point 1.5 cm. from its orifice. Other coronary vessels were patent, although their walls presented areas of thickening and calcification.

The incision in the right inguinal region showed no evidence of infection or hemorrhage. When the peritoneal cavity was opened, no fluid, adhesions, or any other abnormality was noted.

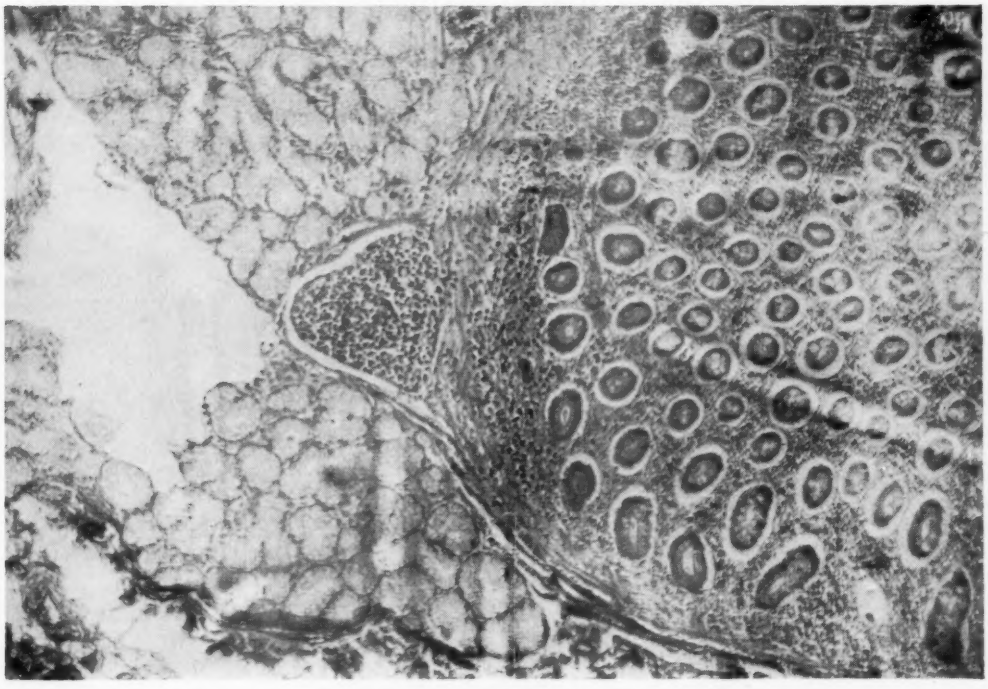

Fig. 2.—Specimen of normal duodenum (×67; reduced ¼) showing typical lymph nodule in the submucosa superficial to Brunner's glands.

The esophagus and stomach were normal. In the first portion of the duodenum there were numerous small "polyps" measuring 0.2 cm. in diameter, and these projected 0.3 cm. above the surface of the mucous membrane. The normal duodenal folds were obliterated. The area covered by the polyps was sharply delineated both proximally and distally, and measured 4 cm. in length. The proximal border was located 0.5 cm. from the pyloric ridge, and the distal border was 3 cm. proximal to the papilla of Vater. No discolorations or ulcerations were noticed in this area. The remainder of the small intestine was normal. In the large intestine there were several true adenomatous polyps which ranged from 0.3 cm. in length and 0.2 cm. in diameter to 1.0 cm. in length and 0.5 cm. in diameter; otherwise the large intestine was normal. The histopathologic examination of the "polyps" in the duodenum revealed that they were composed of hyperplastic lymph nodules of the submucosa.

DISCUSSION

Numerous theories have been advanced to explain the occurrence of lymph nodule hyperplasia. Lehmann[15] and Knoflach[12] regarded the polypoid formation of lymphoid tissue in the rectum and appendix as malformations of a congenital

nature. Nishikawa[18] believed that lymphoid hyperplasia is induced by inflammation, and that it may proceed or remain stationary after the regression of the inflammation. Löffler's[17] hypothesis of a congenital malformation which becomes hyperplastic only in combination with a stimulus, such as inflammation, appears to be most acceptable.

Approximately, 164 cases of lymph nodular hyperplasia of the gastrointestinal tract have been reported; of these, seven were in the stomach,[13, 19] ten were in the appendix,[8, 15, 17, 24, 25] one was in the terminal ileum,[23] one was in the colon,[20] and 145 were in the rectum. In the case here reported, the lymph nodule hyperplasia was limited to the duodenum alone.

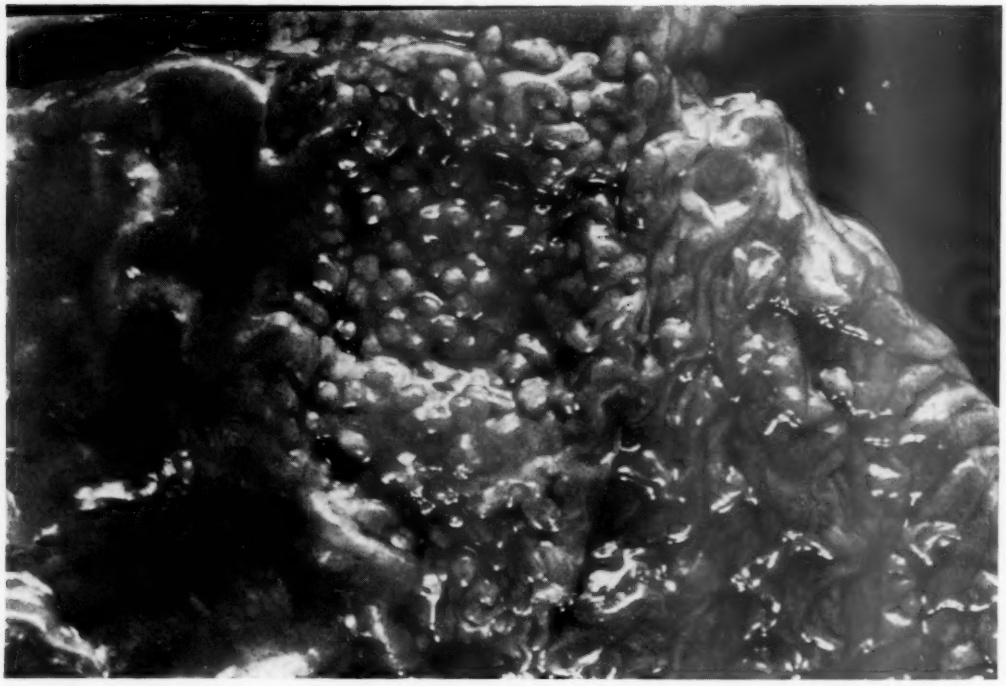

Fig. 3.—Photograph of the mucosal surface of the duodenal bulb showing the numerous papillary projections of the hyperplastic lymph nodules. Note the area of hyperplasia to be sharply delineated proximally by the pyloric ridge and its abrupt cessation 4 cm. distally.

At the time of exploration of the abdominal viscera, the duodenal wall was smooth and normal in appearance; on palpation it was thickened and pebbly due to the polyps projecting into the lumen. The duodenum could be easily separated from the pancreas. In our case the entire mucosal surface of the duodenal bulb was studded with numerous papillary excrescences; approximately 140 individual papillary growths of lymphoid tissue were counted. Schwab[20] has reported similar excrescences involving the colon and rectum. In 36 per cent of the cases of lymphoid polyps of the rectum presented by Li,[16] the lesions were multiple; similarly, in the series presented by Helwig and Hansen[11] the lesions in the rectum were multiple in 40 per cent.

The histologic study of the tissue from the duodenum revealed a noncapsulated, discrete, nodular growth in the submucosa which was supported on a frame of reticular tissue. The cellular elements were composed of lymphocytes which were arranged in patterns that are normally found in the lymph nodules of the intestines. Occasionally mitotic figures could be seen in the germinal centers, and these varied in number among different follicles. The larger nodules compressed the overlying mucosa and thinned it out; in some instances, it ulcerated it. Invasion of the underlying muscular coat did not occur. Associated lymphoid hyperplasia in other organs was not present, and this is an important criterion for the pathologic diagnosis.

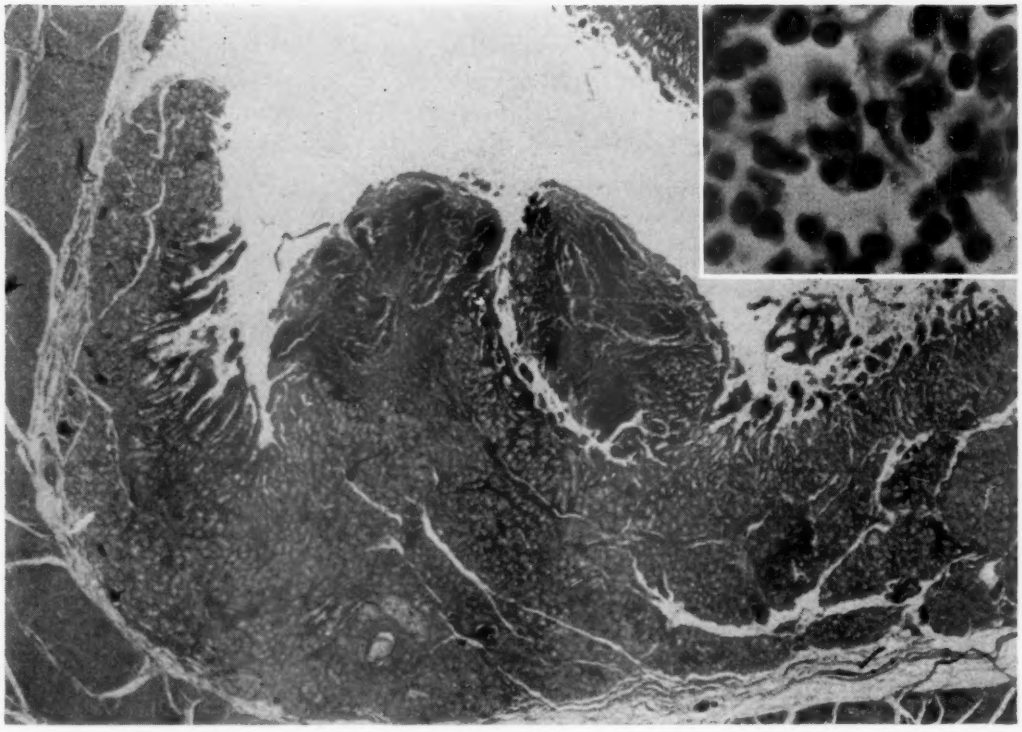

Fig. 4.—Photomicrograph of section of duodenum (×25; reduced ⅕) showing papillary projections of hyperplastic lymph nodules. Note how the overlying mucosa is thinned out over the projections and in some areas appears to be ulcerated.

Inset, Photomicrograph (×600; reduced ⅕) showing a high-power study of cellular elements of a hyperplastic lymph nodule. Note the characteristic lymphocytes enmeshed in a delicate adenoid reticulum.

Lymph nodule hyperplasia of the gastrointestinal tract has been observed by many authors over long periods of time, and in no instance has malignant change developed from one of these nodules. Lymphosarcoma is a nonrelated entity, and may be distinguished by the fact that in this malignancy the growth infiltrates into or through the muscular layer of the gastrointestinal tract.

SUMMARY

A case of papillary lymph nodule hyperplasia of the first portion of the duodenum is presented. This condition has apparently not been reported previously. It is benign, and no malignant changes have been known to develop in

similar lesions elsewhere in the gastrointestinal tract. The roentgenographic appearance is typically that of multiple "buckshot" filling defects in the duodenal bulb.

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THROMBOENDARTERECTOMY, A CLINICAL APPRAISAL

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THROMBOENDARTERECTOMY, an operation described by dos Santos[1] of Lisbon for the definitive treatment of certain types of peripheral arteriosclerosis, has resulted in the development of a new concept in the surgery of peripheral vascular disease. This concept is based upon the finding that the thrombosis of arteriosclerosis often involves a localized segment of a major artery and that it is technically possible to restore normal arterial flow through the occluded arterial segment by surgical resection of the diseased intima. Further clinical experience is necessary to determine the degree to which such an operation may be applied to the entire group of patients with the various syndromes of arteriosclerosis and the factors influencing the morbidity and mortality of the surgical procedure. An extensive study of peripheral arteriosclerosis, with particular respect to the possibilities of thromboendarterectomy in its treatment, has been conducted for the past three years at the University of California School of Medicine and serves as the basis of this report.

There were 187 patients who presented complaints secondary to arteriosclerosis of the peripheral arteries. In 185, the sites of significant arterial disease involved vessels supplying the lower extremities. Aortograms were performed upon 132 patients for the purpose of determining the levels and extent of arterial occlusion. Thromboendarterectomy was attempted in 72 patients. Unexpected findings in the involved arteries made thromboendarterectomy impossible in 10 patients. The complete operation was performed in 62. The criteria used for the selection of suitable candidates for operation included: (1) the presence of disabling symptoms due to arterial occlusive disease; (2) the radiographic demonstration of segmental occlusion of a major artery, either alone or in association with less significant arterial disease at other levels; and (3) a relatively good physical status. The contraindications to operation were: (1) debility of advanced age; (2) the presence of serious concomitant disease status in other organ systems; and (3) the arteriographic demonstration of the diffuse form of arteriosclerosis.

An accurate preoperative demonstration of the extent of significant arterial disease has been the most important criterion for determining the operability with respect to thromboendarterectomy. The translumbar aortic injection of a large volume of Diodrast or Urokon with radiographic exposure of 36-inch films was found to be the most adequate means of obtaining an accurate anatomic visualization of the significant pathologic changes.[2]

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In all patients upon whom thromboendarterectomy was performed, the arteriosclerotic segment involved a portion of the arterial tree between the renal arteries superiorly and the popliteal bifurcation inferiorly. The segmental arteriosclerotic lesions of the 62 patients upon whom thromboendarterectomy was performed were of two types: arteriosclerotic thrombosis and arteriosclerotic stenosis. There were 43 patients in whom the diseased arterial segment was completely occluded. In 35 of these patients, the occluded segment was the only site of significant impairment to blood flow. In 8, secondary levels of occlusive arterial disease, involving the smaller arteries of the leg distal to the popliteal artery or involving the superficial femoral artery with extension beyond the popliteal bifurcation, were demonstrated by aortography. Decision for performing thromboendarterectomy on the latter patients was based upon the possibility of obtaining significant improvement in blood flow by reopening the operable occluded segment at the higher level. The levels of the operable occluded arterial segments are illustrated in Table I.

TABLE I. OPERABLE ARTERIAL SEGMENTS INVOLVED BY ARTERIOSCLEROTIC THROMBOSIS OR STENOSIS

LEVEL OF LESION	NUMBER OF CASES	
	THROMBOSIS	STENOSIS
Aorta	1	2
Aorta and bilateral common iliac artery	14	4
Aorta, bilateral common iliac artery, unilateral external iliac artery and common femoral artery	1	
Unilateral common iliac artery	9	4
Bilateral common iliac artery		8
Unilateral common and external iliac arteries	3	
Common femoral artery	2	
Superficial femoral artery	13	1
Total	43	19

The large number of patients with thrombosis proximal to the inguinal ligament suggests that thromboendarterectomy has had its greatest application to these high-level lesions. Certain pathologic observations may explain the tendency for the segmental nature of high-level thrombosis. The early arteriosclerotic lesion appears as a short zone of intimal thickening which, as it increases in depth, gradually encroaches upon the arterial lumen. This process has been most commonly observed near the orifice of a major arterial branch. Dilatation of the collateral vessels by-passing the stenotic zone is frequently observed in arteriograms taken at this stage. When complete occlusion develops in the stenotic segment, the static column of blood proximal and distal to the level of occlusion clots as far as the level of major arterial branches. Arteriograms taken at this time usually show filling of a major collateral artery at the proximal level of occlusion and a return flow of blood into the thrombosed artery at the lower level of occlusion by reverse flow through the distal collateral artery. It is believed that occlusions in the aorta, iliac artery, and even the common femoral arteries tend to remain localized to a short arterial segment because of the short distance between large arterial branches and the size of these branches. Conversely, occlusions of the superficial femoral arteries tend to be lengthy, extending often from the profunda

femoris to the popliteal artery. An additional observation has been that with occlusion at the aortic and iliac levels, significant arteriosclerotic changes at lower levels are rare, whereas with occlusion at the femoral level, arteriosclerotic changes both proximal and distal to the occluded segment are frequent.

Endarterectomy was performed in 19 patients whose clinical symptoms of ischemia were produced by a segmental zone of arterial stenosis without complete occlusion.[2] Pathologically, such zones of stenosis were characterized by the reduction of the cross-sectional area of the arterial lumen to less than 10 per cent of the normal area. That stenosis of this degree produces critical impairment of blood flow was illustrated by three observations: (1) arterial stenosis of less than the degree indicated, discovered as an incidental finding by aortography or at operation, did not impair arterial flow sufficiently to produce symptoms; (2) the clinical syndromes in those patients with symptomatic stenosis corresponded in most respects to the syndrome produced by complete occlusion at the same levels; and (3) surgical resection of the diseased intima in the stenotic zone resulted in the relief of all symptoms and signs of ischemia in those patients for whom the operation was successfully completed. Three of the patients included in the series of complete thrombosis complained of ischemic symptoms for a short interval before developing complete occlusion. Aortography during the early period had shown arterial stenosis without complete obstruction. The subsequent development of complete occlusion in these patients has suggested that arterial stenosis of sufficient degree to produce ischemic symptoms is an intermediary stage in the development of arterial thrombosis and, as such, constitutes an indication for operation. This opinion was further strengthened by the observation that the difficulties of operation were much greater in cases of arterial thrombosis than in cases of arterial stenosis. There were 2 patients in whom an additional zone of "inoperable" thrombosis distal to the stenotic zone was demonstrated by aortography. The same considerations governed the decision for operation in these patients as were applied in those patients with multiple levels of thrombosis described previously. The levels of the operable stenosed segments are illustrated in Table I.

The average age of onset of ischemic symptoms in the series of 62 patients upon whom operation was performed for segmental stenosis or thrombosis was found to be considerably less than is commonly recognized in peripheral arteriosclerosis. The tabulations of their ages by decades is shown in Table II. Fifty per cent (31) of the patients were under the age of 50 years. The level of the diseased arterial segment was above the external iliac artery in 47 patients. In this latter group, 57 per cent (27) were under 50 years and 13 per cent (6) were under 40 years. The youngest patient was aged 30. The pathologic characteristics, as determined by arteriography, gross inspection at the operating table, and microscopic studies of the resected specimens, were those of arteriosclerosis in all patients. There were no observed pathologic differences between the younger and older age groups.

The symptoms and signs of ischemia produced by the peripheral arteriosclerotic lesions resulted in a variety of syndromes, depending upon the level

of arterial occlusion and the extent of the disease. Where the occlusive process involved only a segment of the arterial tree, manifestations of severe ischemia, such as rest pain and gangrene, were rare. Gangrene produced by solitary obstructions was observed in only 4 patients and rest pain in 3. The occluded segment in these patients was the external iliac artery in 3, the common femoral artery in 2, and the superficial femoral artery in 2. In 4 of these, the onset of symptoms has been sudden, suggesting a solitary acute thrombosis. It is believed that in most of the other patients the progressive development of collateral blood flow produced by the gradual impairment of arterial flow through the main artery minimized the manifestations of the peripheral ischemia. Of the 115 patients who were not operated upon, gangrene or rest pain was observed in 45. In all of these, multiple levels of arterial occlusive disease were found.

TABLE II. AGE OF ONSET OF ISCHEMIC SYMPTOMS IN PATIENTS WITH SEGMENTAL ARTERIOSCLEROSIS

AGE	NUMBER OF PATIENTS
30-39	7
40-49	24
50-59	23
60-69	7
70-79	1
Total	62

The common complaint of all the patients with segmental occlusions was the development of incapacitating muscular symptoms on exercise. Occlusion of the superficial femoral artery or popliteal arteries was associated with calf claudication. Similar calf symptoms were observed with occlusion of the common femoral or external iliac arteries but, because of the interference of blood flow through the profunda femoris, symptoms in the thigh musculature were produced as well. Symptoms in the thigh were rarely those of pain. The more common complaint was severe muscular fatigability or weakness, produced by walking and relieved by rest, and usually localized to the posterior muscle groups of the thigh. Occlusion at the common iliac level produced, in addition to thigh fatigability, similar symptoms in the gluteal muscles. Pain in the low back and hip after exercise was frequently described. These symptoms were believed to arise from decreased flow through the hypogastric artery. When obstruction at this level was bilateral, either from bilateral common iliac or aortic occlusion, impotence in the male was almost universal. This was characterized by the inability to attain or maintain a penile erection. In both sexes, hypesthesia in the perineal area following exercise was an occasional complaint. Arterial stenosis, without complete occlusion, when it was sufficient to produce symptoms, caused complaints which were similar in all respects to those described previously.

The physical findings in cases of segmental arterial occlusion were usually those of minimal ischemia. Muscular wasting was present to some degree in all patients. The specific muscle groups involved corresponded to the level

of arterial occlusion, as described in the preceding paragraph. Muscle atrophy was more profound the higher the occlusion and the longer the duration of symptoms. Pallor of the feet could be produced by exercise or by elevation of the involved extremity. Decrease in peripheral skin temperature was frequently observed, but rarely to more than a few degrees. The presence or absence of peripheral pulses tended to vary with the levels of obstruction. In only one case of femoral artery thrombosis could a distal arterial pulse be palpated and, in this, only at the popliteal level. A peripheral pulse was more readily palpable when the thrombosed segment was at the common iliac or aortic level. In such cases it was the usual experience to palpate a weak pulse in the common femoral artery, due presumably to the large flow through the collateral arteries. In no instance of complete occlusion at this high level, however, were pulses palpable distal to the common femoral artery level. The physical findings in those patients with arterial stenosis varied from this description only with respect to the peripheral pulses. A distal pulse was not palpable in the one patient with superficial femoral stenosis. Femoral pulses were palpable in 15 of the 18 patients with aortic or common iliac stenosis. In 9 of these, even the pedal pulses could be felt. The presence of pedal pulses in such patients frequently had led to previous mistaken diagnosis before the true cause of the patient's complaints was ascertained by aortography. An additional physical finding which often contributed to the correct diagnosis was the presence of an audible abnormal systolic murmur over the artery distal to the level of stenosis. This was most apparent over the femoral artery in those patients with stenosis at the common iliac artery or aorta level. The presence or absence of palpable thickening of the femoral artery, associated with aortic or iliac occlusion, was found to be a significant factor in determining the operability of high occlusions. Although the technical feasibility of iliac combined with femoral thromboendarterectomy has been demonstrated, the experiences of this study have indicated that combined procedures of this extent are rarely successful. The presence of palpable thickening of the femoral artery in patients with iliac thrombosis has usually been shown by subsequent aortography to indicate the advanced diffuse form of arteriosclerosis not amenable to thromboendarterectomy. Tissue necrosis, skin atrophy, edema, and persistent rubor were characteristically found to be associated with multiple occlusive lesions. It was rare to find an operable lesion in patients presenting these findings.

The operative techniques employed for thromboendarterectomy were based upon the method of dos Santos and modified to overcome some of the complications encountered early in the series. Continuous spinal anesthesia has been found to afford maximum relaxation and to reduce many of the hazards resulting from prolonged general anesthesia. The following operative descriptions will refer to thromboendarterectomy as it applies to thrombosis of the terminal aorta. In most respects, the techniques are applicable to arteries at other levels. For exposure of the abdominal arteries, a long paramedian incision extending from the xiphoid to the symphysis pubis is used. The peritoneum is opened anteriorly, at which time manual explora-

tion of the principal arteries is carried out. This is the final stage in assuring the operability of the local lesion. Of particular importance is the determination of the condition of the major arteries distal to the occluded segment. With thrombosis of the aorta or common iliac arteries, the lower level of occlusion has usually been at the bifurcation of the common iliac artery. Diffuse or irregular thickening of the distal patent external iliac artery has been indicative of the diffuse form of arteriosclerosis and may lessen the long-term value of a purely local procedure. The incidence of immediate postoperative thrombosis, either in the operative segment or distal to it, has been highest when there is palpable thickening of the intima distal to the operative area. It has been more common, however, with high occlusions, to find no evidence of significant disease distal to the common iliac bifurcation. With increasing experience in the interpretation of the aortograms, it has become possible to make this differentiation prior to operation.

Exposure of the aorta and common iliac arteries is obtained by incising the posterior peritoneum by a "U" incision around the ascending colon, carrying the left arm of the U to the ligament of Treitz and the right arm to the base of the liver. Blunt dissection in a cephalad direction allows the ascending colon, duodenum, and all of the small intestine to be mobilized in a mass and deposited on the anterior chest wall. For the purpose of reducing postoperative ileus, the viscera are wrapped in a plastic bag after the method suggested by Lahey.[3] The aorta will be exposed by this procedure to the level of the renal arteries. Further exposure of the distal half of the left common iliac artery and the left external iliac artery is obtained by incising the posterior peritoneum lateral to the mesosigmoid along a line parallel to and 5 cm. lateral to the left ureter. The sigmoid colon and its mesentery may then be retracted in either direction.

Mobilization of the thrombosed arterial segment is obtained by sharp dissection. The patent arterial segments proximal and distal to the thrombosed segment are freed for application of the occluding clamps.

When the aorta is thrombosed, the lumbar and inferior mesenteric arteries have often been divided and ligated to gain greater mobility. There have been no vascular or neurological complications from ligating as many as four pairs of lumbar arteries. The inferior mesenteric artery has been divided during thromboendarterectomy or aneurysm repair thirty-two times. In only one instance was the collateral blood supply to the descending colon inadequate. It is recognized, however, that the greater part of the collateral supply to the lower extremities, in cases of aorta thrombosis, arises from the lumbar and inferior mesenteric arteries. Should the aorta or one of the common iliac arteries become thrombosed after operation, preservation of the extremities may depend upon the patency of these collateral channels. For this reason, it is now the practice to occlude major branching arteries only temporarily by means of bulldog clamps. A special aorta clamp with broad, convexed-surfaced, toothed blades is used for occlusion of the abdominal aorta.[4] Potts divisional clamps are used on the external iliac and hypogastric arteries.

After the proximal, distal, and branching arteries have been occluded, the diseased artery is incised longitudinally along the entire length of the thrombosed segment. This incision is extended to open the patent distal artery. Frequently, one wall of the distal artery will be thickened for several centimeters by a tongue of intimal arteriosclerosis. In this case, the arteriotomy incision is extended distally until the lower level of disease is reached.

The distal, incised arterial wall is then opened out to lie flat between the operator's thumb and forefinger. A circumferential incision is made into the intima below the lower limit of gross arteriosclerotic changes. The intimal incision is made for the purpose of gaining the dissection plane within the media. It is accomplished by a cephalad cutting and scraping action of the scalpel blade to create an oblique surface to the intimal shoulder at the distal end of the dissection. Care is taken to prevent separation of the intima from the media distal to the circumferential incision. Under ideal circumstances, the border of the dissection level will be evident, after this part of the procedure has been completed, only as a change in color of the inner surface of the artery. The use of sutures to hold the intima to the underlying media distal to the operative area has not been found necessary.

There were 4 patients in whom thrombosis developed in the operative segment within a few minutes after blood flow was re-established. In 2 of these, it had been impossible to find a zone of normal intima distal to the thrombosed segment. Circumferential incision into the thickened intima had created a projecting shoulder extending into the arterial lumen in each case. This experience has led to the conclusion that the removal of luminal irregularities is of major importance in preventing postoperative thrombosis.

Proximal dissection, once the pathologic cleavage plane has been obtained, is usually performed without difficulty. In the situation of aorta and bilateral common iliac thrombosis, continuous incisions to open the involved arterial segments create an inverted "Y" opening at the terminal aorta. Tight closure of this defect later may be difficult. For this reason, one limb of the Y is not joined. This requires that the media be undermined to remove the specimen. The dissection is carried cephalad until a relatively normal proximal arterial lumen is reached. When this is in the abdominal aorta, the intima is usually grossly thickened proximal to the upper level of occlusion. The intima is cut off abruptly with no attempt to bevel the upper end. The direction of blood flow at this end tends to prevent the further undermining that might result if this method were used at the distal end of the dissection.

Closure of the incised arterial segment is accomplished by the use of a continuous over-and-over suture of 00000 Deknatel through all layers. Frequently, thrombi tend to form proximal to the upper clamp and distal to the lower clamp during this portion of the operation. Before the arteries are finally closed, the clamps are momentarily released to assure the free flow of blood. If clots have developed and are not spontaneously discharged, they may usually be expressed by digital "milking" of the involved artery toward the open segment. The remainder of the artery is then closed and the clamps are released. The distal clamps are released first to allow the operated seg-

ment to fill with blood under low pressure. Bleeding may occur along the suture line which ordinarily ceases within a few minutes. It is often necessary to use additional sutures to close the larger openings. The proximal clamp is then slowly loosened until a normal pulsatile flow of blood is present. Unusual bleeding at this time may be controlled by partially closing the proximal clamp and waiting until the openings close.

After all the clamps are removed, care is taken not to handle the arteries further. Thrombosis may be precipitated by breaking up the thin layer of clotted blood lying upon the inner surface of the artery. In three cases, it was necessary to reopen the closed artery to remove a fresh thrombus which had formed subsequent to manipulation of the artery at this stage.

The method of the use of anticoagulants to overcome the thrombotic complications of thromboendarterectomy has undergone numerous revisions. During the closure of the incised arteries, the lumen of the operated segment is continuously irrigated with dilute heparin solution (10 mg. heparin per 100 c.c. saline solution) to prevent the local accumulation of clotted blood. During the period in which the clamps are in place, there has been a strong tendency for thrombosis to develop in the distal arterial tree. This occurred in 2 unheparinized patients and led to the use of a continuous infusion of heparin into the distal arteries through inlying polyethylene tubes.[5] Heparin was given in proper dilution to prevent systemic heparinization. Following the adoption of this technique, there were no further cases of distal thrombosis following thromboendarterectomy. Thrombosis, however, did occur at the operative area in 4 patients. In each instance, a clot formed within the first hour after restoration of blood flow. In no case did local thrombosis develop after the first hour in the immediate postoperative period.

To overcome the tendency for early thrombosis in the operative area, systemic heparinization is now obtained by the intravenous injection of sufficient concentrated heparin to raise the clotting time to thirty minutes. This usually requires from 15 to 30 mg. of heparin. The injection is made before the clamps are applied and adequate time is allowed for the full anticoagulant effect. Frequent coagulation times are taken to make certain that this level is maintained for an adequate period. In most cases, the coagulation time remains above twenty minutes for at least one hour after the clamps are released. No unusual soft-tissue bleeding has developed with the use of this technique. Greater care must be taken, however, to secure a watertight closure of the arteriotomy incisions. Up to thirty minutes may be required to stop the bleeding from the suture line. The local application of Gelfoam has been valuable for this purpose.

No additional anticoagulant therapy is given during the postoperative period. It is apparent that with this technique, the infusion of heparin into the distal arterial tree was unnecessary and accordingly has been abandoned. The method described has been used successfully in the last fifteen operations in the series. There have been no thrombotic or hemorrhagic complications since its adoption.

Lumbar sympathectomy has been combined with thromboendarterectomy in the last thirty-eight operations, either as a preliminary operation in patients with femoral thrombosis or simultaneously when the abdomen is open for aorta or iliac thromboendarterectomy. This has been done for two reasons: (1) Arterial thrombosis, either as a result of operation or due to the progression of arteriosclerotic changes in other arteries, is a constant hazard. Sympathectomy may avert the more serious complications of ischemia should thrombosis occur. (2) It is also believed that the more rapid the blood flow through the operative segment, the less the likelihood of local thrombosis. Sympathectomy, by lowering the peripheral arterial resistance and thereby increasing the velocity of blood flow, may be of value in decreasing the possibility of local thrombosis at the operative site.

Thromboendarterectomy was attempted, but abandoned after preliminary exploration, in 10 patients, because of unforeseen pathologic changes at the site of thrombosis. In 8 patients, an unusual degree of intimal thickening distal to the thrombosed zone made it likely that postoperative thrombosis would develop, because of the thick ledge of intima which would project into the lumen at the lower border of the dissection, should thromboendarterectomy be attempted. In 2 patients, diffuse inflammatory changes in the periarterial tissue at the site of thrombosis made it impossible to dissect the artery free from the adjacent structures with safety. In both patients, thrombosis had occurred as a sudden event. In one, exploratory operation was performed eight days after the acute episode and in the other at six weeks. Two other patients were operated upon within the first twenty-four hours after an acute thrombosis. Early inflammatory changes were observed in these patients, as well, but not to a degree to prevent safe dissection. On the basis of this experience, it has been concluded that there may be a period of relative inoperability following acute arterial thrombosis, because of the local periarterial inflammatory reaction, and that unless operation can be performed within the first twenty-four hours, it should be deferred until the inflammatory phase has passed.

The mortality rate for the entire series has been 12.9 per cent. In 2 patients, death was due to cerebrovascular thrombosis occurring on the ninth and twentieth postoperative days, respectively. Both patients had fully recovered from operation prior to the vascular accidents. Death was due to renal failure in 2 patients. In both cases, a prolonged period of hypotension had existed during the operation. Death was preceded by the development of a typical lower nephron syndrome in each case. The adoption of adequate blood replacement and the use of vasopressor agents have minimized this hazard. Hemorrhage caused the death of 2 patients, in 1 from disruption of the aorta suture line on the thirty-first day, and in the other on the first day because of bleeding from an undetermined intra-abdominal site. Ligation of the inferior mesenteric artery leading to necrosis of the descending colon and subsequent bowel resection was followed by death in shock in 1 patient. An unconfirmed coronary thrombosis contributed to one fatality. With the improvement in selection of patients and in operative technique, the mortality

has been reduced to 6.4 per cent in the second half of the series. The last 17 patients have been successfully operated upon without a death.

Arterial thrombosis due to operation occurred in 7 patients, occlusion at the operative site in 4 and in the distal arterial tree in 3. The factors contributing to the development of thrombosis have been described in the preceding description of the operative technique. Change in the method of anticoagulant administration and the more careful selection of patients for operation have significantly reduced this complication. Although 2 of the patients subsequently died from other causes, it is significant that in no case did the development of postoperative thrombosis cause a degree of ischemia greater than that which had existed prior to operation. Late arterial thrombosis at the operative site occurring after the early postoperative period has developed in only 2 patients and, in these, one year after operation. In both cases, the site of the original thrombosis was in the superficial femoral artery, and in both cases definite arteriosclerotic disease proximal and distal to the operative zone had been apparent at operation.

Arterial disruption and hemorrhage occurred in 3 patients. In two cases, subsequent arterial ligation was necessary, on the tenth and fifteenth postoperative days, respectively, and was followed by the development of gangrene for which supracondylar amputations were performed. In the third patient, hemorrhage from disruption of the common iliac suture line appeared on the twenty-fifth postoperative day. Immediate repair of the arterial opening was successful. This patient died ten days later from disruption of the aorta suture line. Operative and post-mortem observations have shown that necrosis of the arterial wall at the site of suture, rather than breakage of suture material, was the cause of disruption in each case. It is believed that the use of a reinforcing sleeve of fascia lata applied about those arteries which appear unusually weak will prevent arterial disruption.[6] This technique has been used successfully in fifteen operations. It was not used in the patients who developed arterial disruption. Close observation for three to five weeks following operation and immediate repair, should sudden hemorrhage develop, may also reduce the hazard of arterial disruption.

Gangrene requiring leg amputation occurred in 4 patients. In one, the patency of an acutely obstructed external iliac artery had been successfully restored by thromboendarterectomy. The preoperative line of demarcation descended from the mid-thigh level to the ankle following operation, but irreversible changes in the foot required later amputation. In another, amputation was necessary for the treatment of acute gas bacillus infection superimposed upon pre-existing gangrene of the toe. Arterial ligation for the control of arterial disruption led to amputation in the other 2 patients, 1 of whom subsequently died from coronary thrombosis.

The tabulation of the operative results of thromboendarterectomy with respect to patency of the arterial tree and clinical improvement is recorded in Table III. The 54 living patients have been followed for periods varying from three to thirty months. Thirty-two of the patients have been followed for over one year after operation and 11 for over two years. The immediate

postoperative result has been sustained in all but the 2 patients noted previously who developed recurrent thrombosis one year after operation. There have been 45 patients (72 per cent) who have demonstrated persistent circulatory improvement. Thirty-six of these have regained normal peripheral circulation as evidenced by the restoration of all peripheral pulses, the healing of gangrenous lesions (4), the relief of rest pain (4), and the absence of all muscular symptoms on exercise. Sexual potency, as gauged by the ability to maintain a normal penile erection and to experience the subjective sensation of orgasm, was restored in 12 of the 18 patients presenting this complaint. It is to be noted, however, that ejaculation function was destroyed, presumably because of the necessary division of the preaortic autonomic nerves. There were 9 patients who, because of the presence of secondary thrombosis distal to the operative area, did not regain a normal circulatory status. Definite improvement in the signs and symptoms of ischemia followed the restoration of patency of the proximal occluded segment. Of the 47 patients whose circulation was either restored or improved after operation, 8 had previously been treated by lumbar sympathectomy. The circulatory improvement obtained from thromboendarterectomy greatly exceeded that obtained from sympathectomy.

TABLE III. OPERATIVE RESULTS OF THROMBOENDARTERECTOMY—62 CASES

	PEDAL PULSATIONS RESTORED	PEDAL PULSATIONS NOT RESTORED		
		PREOPERATIVE DISTAL THROMBOSIS	POSTOPERATIVE DISTAL THROMBOSIS	POSTOPERATIVE LOCAL THROMBOSIS
No signs or symptoms of abnormal peripheral circulation	38			
Peripheral circulation improved		7	2	
Peripheral circulation unchanged				4
Amputation	1	2		
Died	6	1	1	
Total	45	10	3	4

SUMMARY

Thromboendarterectomy has been performed in 62 patients for the treatment of segmental arteriosclerotic thrombosis or stenosis of major arteries. A normal or improved arterial circulation has been restored in 47. The factors influencing the selection of suitable candidates for operation are discussed. The adoption of improved operative techniques has led to a gradual reduction in mortality and the incidence of complications.

ADDENDUM

Subsequent to the preparation of this report, thromboendarterectomy has been performed on eleven additional patients. A successful result was obtained in ten, all of whom had thrombosis or stenosis of the terminal aorta and common iliac arteries preoperatively. In the eleventh patient, operation was performed for thrombosis of the common and external iliac arteries. The postoperative development of thrombosis in the operative segment in this patient supports the opinion that patients with this degree of arteriosclerosis are not suitable candidates for thromboendarterectomy. There were no further operative deaths.

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DIVERTICULUM APPROACH TO THE HEART CHAMBERS: REPAIR OF DEFECTS IN THE CARDIAC SEPTA BY A MANY-TAILED PLAQUE TECHNIQUE*

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THIS investigation has been carried out to explore the possibilities for repair of defects of the cardiac septa in the functioning heart. Relatively easy and safe access to the cardiac chambers and great vessels is afforded by use of a rubber diverticulum.[3] Through it prolonged digital exploration and instrumentation can be accomplished without significant blood loss.†

INTERVENTRICULAR SEPTAL DEFECT

We have attempted repair of the experimentally produced interventricular septal defect in the dog by several techniques. These have been of two general types, those using a plug of tissue and those using a plastic prosthesis.

Tissue plugs were fashioned usually from segments of inverted homologous aorta, either fresh or preserved (frozen-dried).[5] Physiologic studies revealed that the initial closure of the septal defect was satisfactory using this technique, but after a time the grafts began to disintegrate. On the basis of our experiments, this technique did not warrant clinical application by us, although a similar technique had been used with varying success by others.[1]

Attention was then turned to the use of a plastic button or paddle to occlude the septal defect. A dumbbell-shaped plug made of polyethylene and a paddle of Teflon somewhat similar to that used by Taufic and Lewis[14] were employed in experiments on a group of six dogs. Major difficulty was encountered in anchoring these prostheses so as to occlude the defect, and these techniques were also abandoned. A technique was then developed whereby a flat disk of prosthetic material could be fixed in place by means of several extensions from its periphery so as to occlude defects in the cardiac septa. These peripheral extensions from the disk were designed to be passed out through the septum and anchored on the epicardial surface of the heart (Fig. 1). The technique presently described differs from similar attempts to occlude septal defects by various materials passed through the ventricular septum as described by Murray[11] and King.[10]

METHOD

Unselected mongrel dogs were prepared by creating a high interventricular septal defect under Nembutal anesthesia. The cork-borer and suction technique,

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†Manufactured by Seamless Rubber Co., New Haven, Connecticut, in three sizes (based on the diameter of the base), Small, Medium (Standard), and Large.

previously described by Kay, Thomas, and Blalock,[8] was used to produce defects approximately 7 or 9 mm. in diameter. All dogs had a prominent systolic thrill over the right ventricle and an accompanying loud systolic murmur after production of the defect. Rapid digitalization was accomplished prior to or just after creation of the defect and was maintained until repair in the surviving animals. Cardiac catheterization was performed before creation of the defect and before and after repair of the defect. A stethocardiogram preceded and followed each procedure and in some experiments was recorded at intervals during the postoperative period.

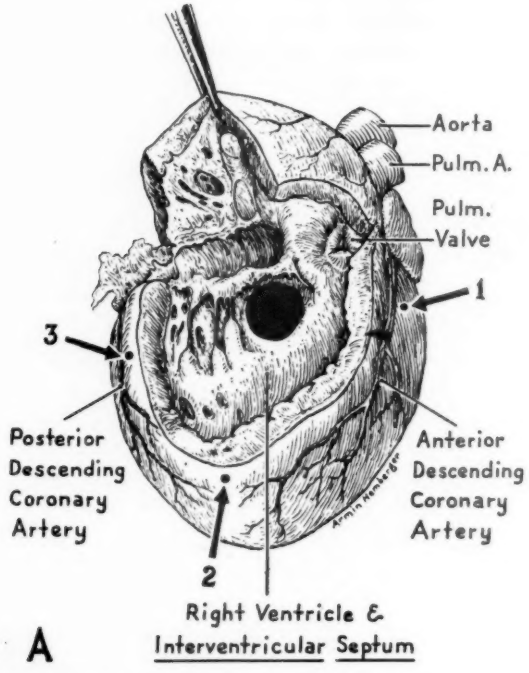
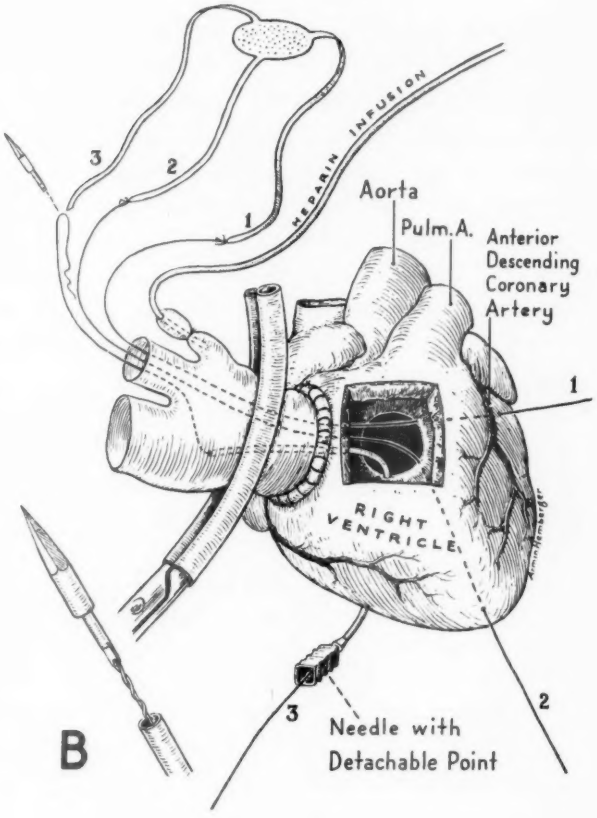


Fig. 1.—Technique of plaque repair.
***A*, High interventricular septal defect showing points of entrance of the detachable-point needles.**

The plastic plaques used in the repair of the ventricular defects were cut from sheets of polyethylene approximately 0.1 mm. thick. Three tails of plastic were fashioned to extend from the periphery of a central disk at approximately equidistant points. The tails were further thinned out by applying traction after gentle heating of the polyethylene. The tails so prepared measured about 12 to 15 cm. in length, about 2 to 3 mm. in width, and 0.025 to 0.05 mm. in thickness (Fig. 1, *B*).

Repair of the defect was accomplished after opening the chest through a transsternal fifth intercostal space incision. The right ventricle was entered through a rubber diverticulum sutured snugly to the myocardium. A needle with a detachable point[4] was threaded with a small wire suture, and three of these were passed sequentially into the myocardium at approximately equidistant points around the circumference of the interventricular septum. All needles were passed in the plane of the interventricular septum and emerged



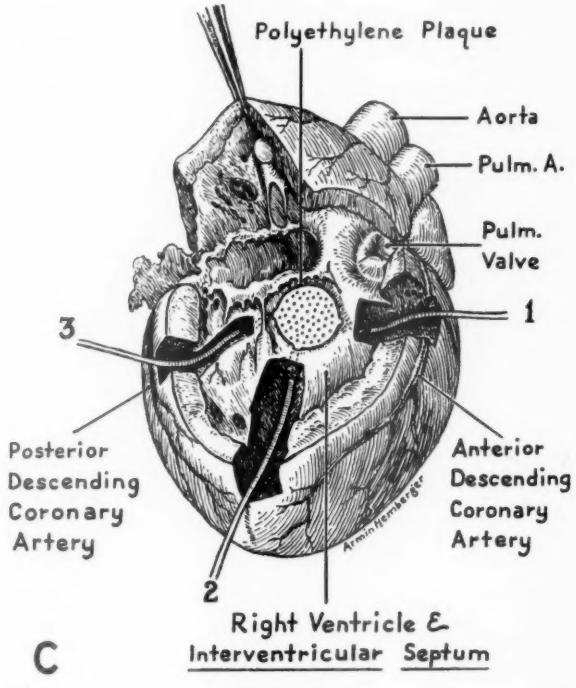


Fig. 1 (*Continued*).

B, Diagrammatic representation of the essential steps of the many-tailed polyethylene plaque technique in repair of the interventricular septal defect. The inset shows the detail of the detachable-point needle.

C, The polyethylene plaque in place held by the three tails.

from the edges of the defect, guided by an exploring finger in the right ventricle. The needle points were then directed into the rubber diverticulum and the points detached, leaving the three wires in place as the needles were then withdrawn. The wires were then attached to the tails of the polyethylene plaque and traction on each of the wires was applied, pulling the polyethylene plaque through the diverticulum and into the defect (Fig. 1). Suture ligatures served to anchor the tails at their points of exit on the epicardial surface of the heart. Usually the plaque would nearly close the septal defect, although there was always some leakage of blood around the plaque from the left ventricle into the right. During systole this jet of blood from the left ventricle could easily be appreciated by the finger in the right ventricle.

RESULTS

An attempt was made to repair the interventricular septal defect by means of a polyethylene plaque in seventeen dogs. Of these, three died in ventricular fibrillation during the procedure. Three others succumbed in the first three days postoperatively of infection, failure of repair, and unknown causes, respectively. The outcome of the remaining eleven animals which survived beyond one week is recorded in Table I.

TABLE I. REPAIR OF THE INTERVENTRICULAR SEPTAL DEFECT WITH POLYETHYLENE PLAQUE

EXP. NO.	DURATION OF DEFECT (DAYS)	TIME RIGHT VENTRICLE OPEN (MINUTES)	SIZE OF DEFECT (MM.)	SURVIVAL TIME (WEEKS)	COMMENTS
78	7	52	7	17	Sacrificed; defect closed
85	16	41	7	1+	Died under anesthesia for catheterization; defect closed
88	7	64	7	12	Sacrificed; 2 by 3 mm. defect still open
90	12	69	7	12	Sacrificed; defect closed
92	9	42	7	10	Sacrificed; defect closed
94	7	42	9	7	Sacrificed; defect closed
95	12	54	9	2	Died of sepsis; defect open widely
98	7	—	9	4	Sacrificed; streptococcal endocarditis; defect closed
102	2	73	9	7	Died; cause unknown; small residual defect
104	2	77	9	4	Sacrificed; two wound dehiscences; multiple arterial emboli; thrombi in heart
108	10	55	7	13	Sacrificed; defect closed; abscess formation around 2 of the tails

Electrocardiographic changes following high interventricular septal defect production in twenty-five consecutive dogs are tabulated in Table II. Electrocardiographic tracings were made immediately before and after creation of the defect, and at intervals during the two to fourteen days before attempted repair. Right bundle intraventricular block was by far the most common abnormality found. It was interesting that in no instance was any

significant injury current evident. Electrocardiographic changes following the repair were usually not of major significance. Occasionally an intraventricular block became slightly worse with repair, and once there was some right axis shift with repair. One dog, dying about two hours after repair, did show definite injury current in an electrocardiogram shortly before death. In Experiment 98, evidence of septal infarction was apparent in an electrocardiogram taken at about four weeks after repair, at which time this animal had acute bacterial endocarditis.

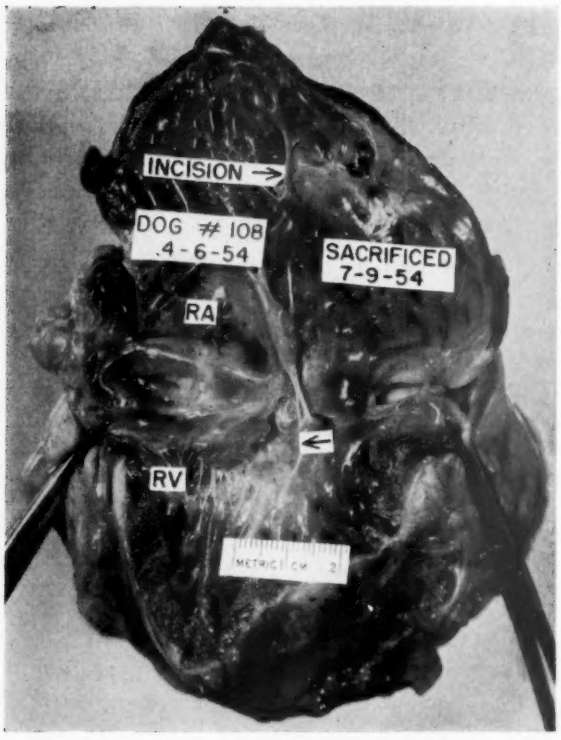
TABLE II. ELECTROCARDIOGRAPHIC FINDINGS AFTER HIGH INTERVENTRICULAR SEPTAL DEFECT PRODUCTION IN TWENTY-FIVE DOGS

ELECTROCARDIOGRAPHIC FINDING	NUMBER OF OCCURRENCES
Complete atrioventricular block	2
Incomplete atrioventricular block	1
Right bundle block	20
Left bundle block	1
Frequent ectopic premature beats	2
Pericarditis	1
Normal	2

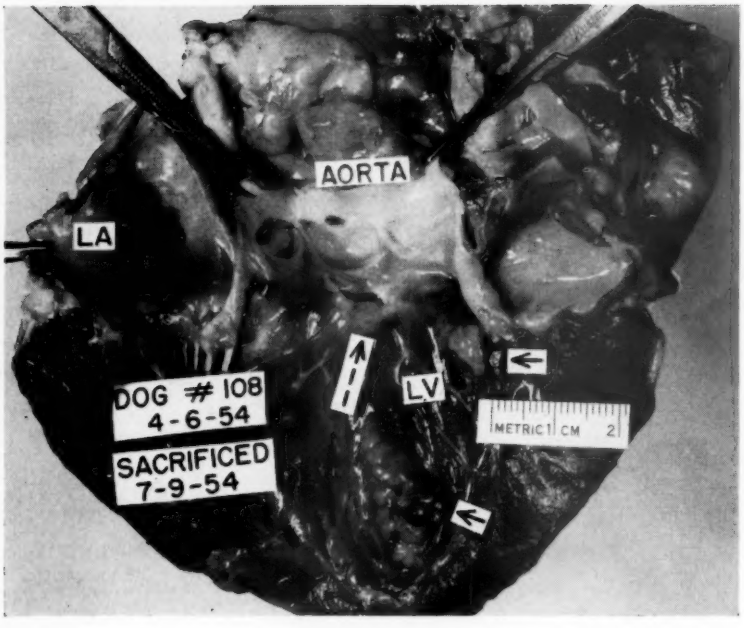
We are aware, of course, that the experimental interventricular septal defect of the size produced will frequently close spontaneously. However, these defects served our major purposes, which were to study (1) the operative approach through the diverticulum, (2) the response of the functioning heart to the placement of the plaque, (3) the immediate effect of the plaque on the right-to-left shunt, and (4) the tolerance of the myocardium to the plaque.

As noted in Table I, six of these animals were sacrificed in good health between seven and seventeen weeks after repair. These and two others which died, one after anesthetization for cardiac catheterization after eleven days and the other at seven weeks from unknown causes, will be discussed together. The interventricular septal defect was completely closed in six of these eight animals and was greatly reduced in size (2 to 3 mm.) in the remaining two. On gross inspection of the interventricular septum of these hearts at autopsy, usually only a smooth, blanched area of scar was visible in the region of the repaired defect (Fig. 2). Occasionally, however, a small protruding portion of the plaque or of one of the tails was not covered over by endocardium, and sometimes there was a mound of granulation tissue around the exposed polyethylene. When the plaques were dissected out, all portions of the tails which were buried within the myocardium were found to be contained in a capsule of fibrous tissue. Microscopic sections through these areas showed a dense sheath of mature fibrous tissue, usually without inflammatory reaction. In sections through those areas where the polyethylene was exposed directly to the circulating blood, generally the plaque was covered by a much thicker layer of fibrous tissue. In areas where grossly the granulations were seen surrounding the uncovered portions of the plaque, there was acute and chronic inflammatory change microscopically.

Freedom from sepsis may be an important prerequisite to the deposition of a film of fibrin over the plaque. The plaque shown in Fig. 3 was in place for only three days and is seen to be completely covered with fibrin, although it



A.



B.

Fig. 2.—Experiment 108. Interventricular septal defect.

***A*, Photograph of right ventricular aspect of interventricular septal defect repaired with plastic plaque. The area of the interventricular septal defect is indicated by the arrow.**

***B*, View of left ventricle showing the closed defect (dotted arrow) and areas of reaction (abscess) surrounding portions of the plaque tails (solid arrows).**

does not totally occlude the defect. On the other hand, in the one animal (Experiment 95) dying of overwhelming sepsis two weeks after repair, there was no tendency for the plaque to be covered, and the defect showed no evidence of healing grossly. This animal is of further interest inasmuch as he was in ventricular fibrillation three times: once fibrillation occurred during creation of the defect, again just after opening the chest to repair the defect two weeks later, and the third time immediately following the repair. Unsterile electrodes were used on the last occasion to defibrillate the ventricles. The remaining two animals were sacrificed in poor condition at four weeks. One of these had clinical signs of saddle embolus to the aortic trifurcation and gastrointestinal tract embolization. At post-mortem this heart contained thrombi in all chambers, and there were multiple peripheral emboli in addition to those apparent clinically. The other dog had an acute bacterial endocarditic process at two points where polyethylene tails penetrated into the left ventricular chamber and also on the mitral valve leaflets. There was also a perforation of the aortic leaflet of the mitral valve either due to the endocarditis or possibly to trauma at the time of production of the defect.

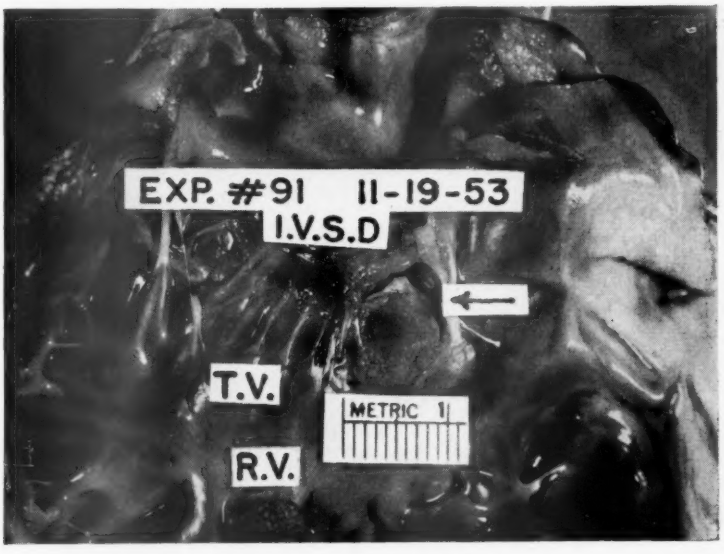


Fig. 3.—Experiment 91. Interventricular septal defect. Photograph of right ventricular aspect of an interventricular septal defect partially closed by polyethylene plaque. This plaque, in place for three days, is covered completely by a fibrin deposit.

In none of the repairs was there any encroachment on the chordae tendineae of the tricuspid valve by the plaque. No tendency was noted for the plaque to migrate, nor was there any fragmentation of the plastic. There was no evidence of cyst formation about the polyethylene and, when buried within the myocardium, it seemed to be well tolerated by the heart, in the period of time covered by this study. Obviously, this study gives no indication of the reaction of tissue to this plastic after long-term exposure.[13]

Stethocardiographic tracings revealed that the systolic murmur present after creation of the interventricular septal defect became less pronounced

after repair. In some of the animals with persistent soft murmurs, and in one whose murmur was moderately loud (Grade iii), there was no residual defect at post-mortem examination. These murmurs were probably due to tricuspid insufficiency inadvertently created at the time of production of the interventricular defect, since many of these dogs had a palpable thrill over the right auricle, as well as over the right ventricle subsequent to the removal of a plug of myocardium from the upper interventricular septum.

Blood oxygen and pressure studies from the right heart (Table III) indicated a moderate left-to-right shunt following the creation of the defect. Although there was noted some probable decrease in the shunt immediately following repair of the defect, in general it was not as striking as that observed following the tissue plug type of repair.[5] It is obvious, from the catheterization data and the palpation of a residual jet at operation, that the repair of the ventricular septal defect with the polyethylene plaque did not result in complete closure immediately.

TABLE III. REPRESENTATIVE CARDIAC CATHETERIZATION STUDIES ON LEFT-TO-RIGHT SHUNT THROUGH THE INTERVENTRICULAR SEPTAL DEFECT*

EXP. NO.	TIME OF CATHETERIZATION (DAYS)	BLOOD OXYGEN PER CENT SATURATION			INTRACARDIAC PRESSURES (UNCORRECTED) (MM. HG)		
		RA	RV	PA	RA	RV	PA
88	3 days before IVSD	62.0	60.8	59.5	—	—	—
	3 days after IVSD	69.4	78.2	71.8	12/0	30/0	30/10
	9 days after repair	65.4	70.70	68.7	—	—	—
	87 days after repair	73.0	73.0	77.8	12/-1	37/3	37/15
90	Immediately before IVSD	81.5	85.5	87.0	—	—	—
	5 days after IVSD	51.9	62.2		10/4	44/-4	44/9
	8 days after repair	36.68	42.70	40.80	19/-2	44/-2	35/7
	92 days after repair	42.3	42.3	42.3	6/2	32/5	—
94	3 days before IVSD	70.51	71.43	66.7	4/-1	25/-1	30/18
	4 days after IVSD	53.5	59.5	69.8	15/6	25/-1	25/10
	6 days after repair	59.2	60.4	66.4	—	27/-2	27/6
	46 days after repair	68.5	69.70	70.05	10/0	27/-1	22/6

*Repaired with polyethylene plaque.

INTERATRIAL SEPTAL DEFECT

Repair of the experimentally produced interatrial septal defect through a rubber diverticulum sewed to the right atrium was attempted in seven dogs. A defect in the septum between the two atria about 2 cm. in diameter was made one to four weeks prior to the attempted repair.

METHOD

A rubber diverticulum was sewed to the edges of a right atrial incision with two continuous sutures of fine (0000) arterial silk. A heparin drip was started and the index finger inserted through the diverticulum and atrial incision into the chamber of the right auricle. The soft portion of the interatrial septum was palpated just behind the aorta. The ostium of the coronary sinus was identified and a stab wound made between it and the aorta into

the chamber of the left atrium. This incision was enlarged by digital dilatation and use of intracardiac scissors to its maximum size. During all intracardiac manipulations, a specially made glove was worn. This glove* is extremely thin and offers nearly the tactile advantages of the naked finger but at the same time assures aseptic technique in the intracardiac manipulations. In addition, the rubber-covered finger slides much more easily into and out of the diverticulum and the myocardium.

After the defect was made, the diverticulum was removed and the atrial incision closed. The animal was then allowed to recover. One to four weeks later a second thoracotomy was performed, and a second diverticulum was sewed onto the right atrium in the region of the previous incision. The septal defect was then palpated and repair of the defect carried out.

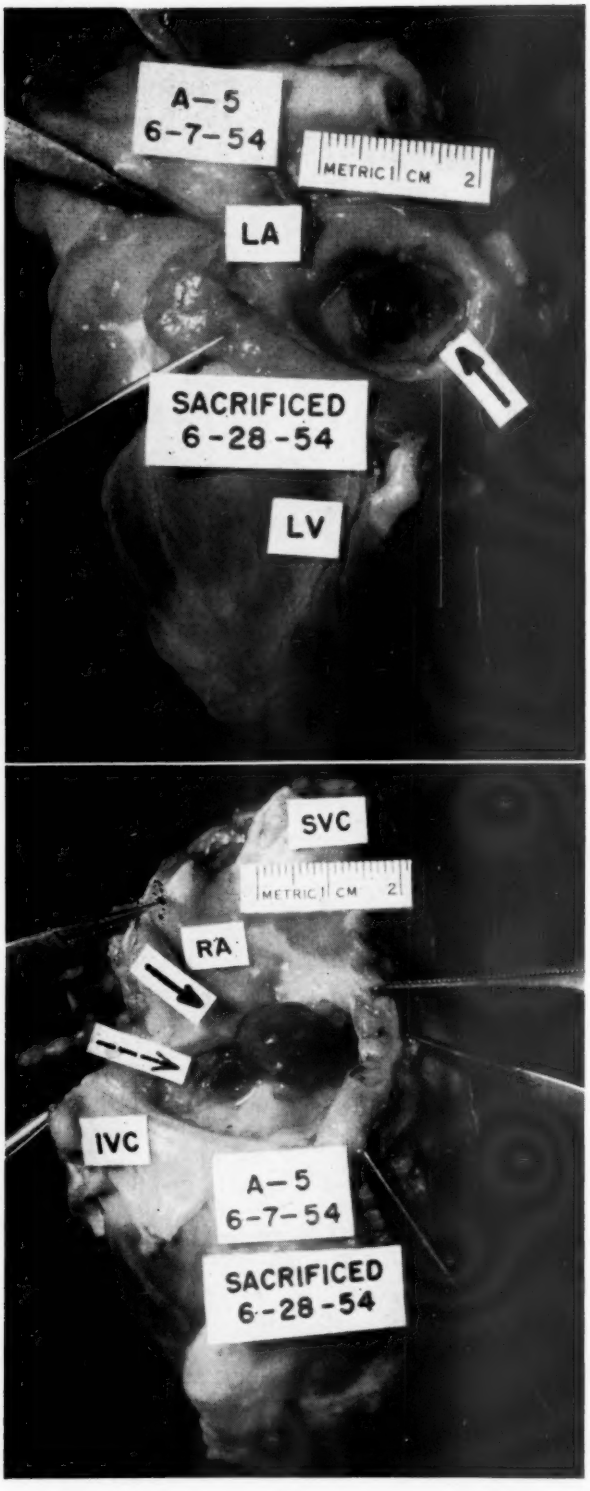
The plaque technique, as previously described, was also used to close the interatrial defects. In one animal, a frozen-dried homologous cornea was used to close the defect. It was held in place by four fine braided wire sutures similar in function to the tails on the polyethylene plaque. The plaques were placed in the atrial septal defects in the same way that they were placed in the interventricular septal defects. The needles with detachable points were inserted into the septal defect from outside of the heart through the substance of the auricular septum. Because of the thinness of the interatrial septum, perforations by the needle were common, resulting in a weaving of the tails in and out of the left and right atrial chambers. An attempt was always made to place the plaque so that it would lie in the left atrium. The higher pressure in the left atrium we felt would favor compression of the plaque against the margins of the defect. Because the atrial septal defects were considerably larger than the ventricular defects, four tails were sometimes used instead of three to hold the plaque in place. One of these made its exit from the auricle above the coronary sinus; a second one at the junction of the auricular septum with the superior vena cava; the third at the posterior superior portion of the septum near the aorta. The fourth pierced through the posterior inferior interatrial septum and passed through the interventricular septum. It was anchored on the right ventricular side of the anterior descending coronary artery about two-thirds of the way down the anterior surface of the heart. Following repair of the defect, the diverticulum was removed and the wound in the atrium was closed.

RESULTS

Repair of the interatrial septal defect by the plaque technique was attempted in five animals. In one of these the defect had closed spontaneously, and the animal did not survive the creation of a second defect with immediate repair. The remaining four animals survived repair of the atrial defect and were sacrificed about three weeks later. The results of the repair in these experiments are shown in Table IV and Fig. 4.

*Made by the Seamless Rubber Co. and known as a "Cardiac Surgery Glove."

A.



B.

Fig. 4.—Experiment 1. Interatrial septal defect.

A, View of left atrial side of interatrial defect showing plaque completely covering the defect, indicated by the arrow.

B, Right atrial view showing thrombus covering part of defect (solid arrow) and granulation tissue surrounding a sinus tract which leads to the polyethylene plaque beneath it (broken arrow).

TABLE IV. INTERATRIAL SEPTAL DEFECT

EXP. NO.	CREATION TO REPAIR INTERVAL (DAYS)	APPROXIMATE DIAMETER OF DEFECT AT REPAIR (CM.)	TECHNIQUE OF REPAIR	POSTREPAIR SURVIVAL TIME (DAYS)	CAUSE OF DEATH	REMARKS
1	21	2.0-2.5	Polyethylene	21	Sacrificed	Defect closed
2	21	0.5-1.0	Polyethylene	21	Sacrificed	Defect closed by plaque
3	19	0.0 (New 1.5 cm. defect made)	Polyethylene	0	Ventricular fibrillation	Original defect closed; new defect made and repaired at same procedure
4	7	1.5-2.0	Polyethylene	28	Sacrificed	Small residual defect
5	9	1.5-2.0	Cornea	26	Sacrificed	Small residual defect

DISCUSSION

It is difficult to know at the present time what method of closure will eventually be preferred for defects of either the atrial or ventricular septa. In brief, the closure of septal defects in the heart has been accomplished by several investigators, both in the laboratory and in the clinic, by either direct suture with approximation of the edges of the defect or by attachment of a plug or graft of tissue or plastic. The method of approach to the cardiac chambers to effect the repair may permit visualization of the lesion or may be accomplished by palpation. In the majority of the uncomplicated atrial septal defects, closure either by direct suture,[15] sometimes aided by hypothermia[2] or by a method utilizing a part of the atrial wall in the repair,[12] has been successful. It is difficult for us to conceive, in the light of our present knowledge, that eventually the indications for closure of the interauricular septal defect will be simply "the diagnosis of the uncomplicated anomaly"[2]; yet the strides in intracardiac surgery are so rapid as to suggest this as a possibility.

The congenital defect in the septum primum (Fig. 5) of the atria or the high (membranous) defect of the ventricular septum, particularly with overriding of the aorta, would appear to defy direct suture techniques due to the proximity of the valve cusps as well as vascular and impulse-conducting structures in the myocardium. Such defects may always require grafting techniques similar to those reported in this paper. It would seem important in determining the proper placement of these grafts to explore the septal defect in its dynamic state. It would also appear likely that grafting techniques may be performed equally well and with considerably less risk in the functioning heart. This last statement requires confirmation, as too little is known at present about the repair of these types of defects. A technique requiring puncture of the ventricular septum is dangerous, as the septal artery[9] or the conduction bundle may be injured. With regard to the conduction tissue, reference has been made (Table II) to the changes in the electrocardiogram following creation of the high ventricular septal defect. These changes were permanent and persisted as long as the animals survived. Further change in the electrocardiogram after repair of the ventricular defect by the "many-tailed plaque" technique was relatively uncommon. There were in addition,

however, three animals which died of ventricular fibrillation and one other which was successfully defibrillated during repair of ventricular septal defects using the technique described. The relative merits of the visual and the palpatory approach to the repair of any septal defects remain to be determined.

We are not satisfied with polyethylene as a plaque material for closure of interventricular or interatrial defects in the dog. The polyethylene plaques usually were fitted easily into place in the septal defect, but there was occasionally excessive thrombus formation on the surface of the plastic, manifest in some experiments by excessive fibrous tissue organization some months after implantation. Sometimes coverage of the plastic surface exposed to the circulating blood was incomplete. Severe infection in the tissues surrounding the plastic was also observed in occasional experiments. We believe that ideally the material used as a graft either should have a blood supply of its own[7] or should be completely inert.

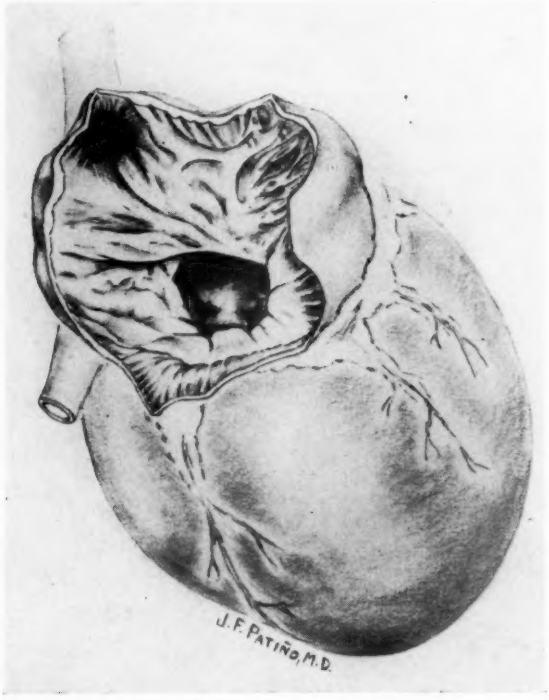


Fig. 5.—Septum primum atrial defect. Drawing of right atrial side of autopsy specimen showing a large septum primum interatrial septal defect. Portions of the upper interventricular septum and the mitral and tricuspid valves can be seen just at the inferior margin of the defect.

We continue to be impressed by the simplicity of the diverticulum approach to the chambers of the heart and great vessels. It permits prolonged (more than two hours in some animals) exploration of the heart chambers and, most important, it allows for an examination and repair of a defect with the heart in a dynamic state. Whether these advantages outweigh those of the more complicated but visual approach using hypothermia or an extracorporeal circulation is a matter for further careful study.

SUMMARY

A method for the experimental closure of interventricular and interatrial septal defects by means of a many-tailed plaque fixed to the epicardial surface of the heart has been described. Satisfactory digital and instrumental approach to these defects in the functioning heart was gained through use of a rubber diverticulum. Results are reported from implantation of polyethylene plaques to repair defects of the atrial or ventricular septum in twenty-two experimental animals. The need for selection of a better plaque material and the preliminary steps in this direction have been indicated. The further pursuit of this study is indicated by the need clinically for a method of closure of the high ventricular septal defect, especially with overriding of the aorta, and defects of the septum primum of the atria.

Acknowledgment.—We would like to express our appreciation for the technical assistance rendered by Dr. James M. Shannon, Mr. Armand Negri, and Miss Leah White during these experiments.

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CLINICAL OBSERVATIONS ON THE USE OF ALPHAPRODINE (NISENTIL) FOR POSTOPERATIVE ANALGESIA

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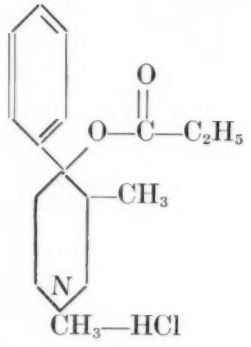
ANESTHESIOLOGISTS and surgeons are constantly searching for analgesic drugs which will produce maximal pain relief with minimal serious or unpleasant side effects. In recent years, many derivatives of piperidine have been studied for their analgesic qualities. One compound which seemed to have considerable merit was alphaprodine (Nisentil).† Clinical studies[1-5] by investigators using Nisentil as an analgesic during the first stage of labor revealed it to have good pain-relieving properties with only slight side effects. The purpose of this paper is to review the effectiveness, safety, and clinical suitability of Nisentil as an analgesic agent in the treatment of pain associated with postoperative surgical conditions.

CHEMISTRY AND PHARMACOLOGY

Nisentil is a synthetic piperidine derivative with the chemical formula dl-alpha-1,3 dimethyl-4-phenyl-4-proprionoxy piperidine hydrochloride. Structurally the formula is:



Ziering and Lee[7] and Holland and Gross,[8] employing the Wolff-Hardy technique or modifications of this method, showed Nisentil to have somewhat less analgesic potency than morphine. Nisentil produced fewer side effects than morphine.[9, 10] Studies on former morphine addicts revealed Nisentil to have addiction liabilities.[11] Numerous clinical investigators[1-3, 12] were sub-

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†Supplied by Hoffmann-La Roche, Inc., Nutley, New Jersey.

stantially in agreement that the onset of action of Nisentil was rapid (three to fifteen minutes) and its duration of action relatively brief (one and one-half to two and one-half hours).

Objectionable side effects (nausea, vomiting, diaphoresis, and respiratory depression) were found to occur in only a small percentage of patients and were only transient in the cases where they appeared.

MATERIAL AND METHODS

The effects of Nisentil were compared in this study with those of meperidine as a postoperative analgesic. Complications and side effects were also observed. There was no specific selection of patients for this study other than that they were all adults who were scheduled to undergo a surgical procedure. All patients were premedicated with sodium phenobarbital, 60 to 120 mg., and atropine sulfate or scopolamine hydrobromide, 0.3 to 0.4 mg., one hour preoperatively. Intravenous, inhalation, spinal, or a combination of these anesthetic techniques was used in all cases. Following the completion of the operation, a study sheet was attached to the patient's chart. The patient's name, hospital number, age, sex, weight, premedication, type and duration of anesthesia, and operative procedure as well as the dosage of the analgesic drug being studied were indicated on this record. The floor nurse was instructed to enter the time each dose was given and to note the time of onset of its effect and the degree and duration of its analgesic action. All side effects were also carefully recorded. No analgesic drug was given unless the patient complained of pain and requested relief. Those patients requiring no therapy were discarded for purposes of this study. The pain relief was recorded as (a) marked, when the patient had no pain for the anticipated duration of the effectiveness of the drug (two hours for Nisentil and four hours for meperidine), (b) moderate, when satisfactory pain relief was obtained for less than these time periods, (c) slight, when only partial pain relief was obtained and even that degree of analgesia lasted less than the anticipated time, and (d) none. Side effects were obtained both by objective signs as seen by the nurses and subjective complaints volunteered by and elicited from the patients. The following side effects were looked for: nausea, vomiting, diaphoresis, dizziness, weakness, headache, pruritus, mental confusion, and respiratory depression. Both drugs were administered subcutaneously.

RESULTS

There were 478 patients studied in this series. One half of them received Nisentil and one half received meperidine. The dosage of the drug was determined on the basis of Nisentil being approximately twice as potent as meperidine. Dosage varied from 30 to 60 mg. for Nisentil and 50 to 100 mg. for meperidine. The same surgeons and anesthesiologists treated both groups of patients.

The age and sex distributions of the patients are shown in Table I. No attempt was made to match these factors for the two groups, but the results

show that there was no appreciable difference in age or sex distribution in the two series. None of the patients in the 11-20 year group was under 17 years old. The oldest patient was 74 years old.

TABLE I

	NISENTIL				MEPERIDINE			
	MALE		FEMALE		MALE		FEMALE	
AGE (YR.)	NO.	%	NO.	%	NO.	%	NO.	%
11-20	6	2.6	7	3.0	5	2.2	5	2.2
21-30	14	5.8	19	7.9	15	6.2	19	7.9
31-40	19	7.9	22	9.2	21	8.8	25	10.4
41-50	28	11.7	33	13.8	30	12.5	25	10.4
51-60	27	11.3	38	15.8	28	11.7	33	13.7
61-70	11	4.6	11	4.6	14	6.0	16	6.7
71-80	2	0.9	2	0.9	1	0.4	2	0.9
Total	107	44.8	132	55.2	114	47.8	125	52.2

The results of the analgesic effects of the drugs are summarized in Table II. Nisentil has approximately the same pain-relieving ability as meperidine when given in equivalent therapeutic doses. In both groups, more than one-half the patients received marked relief and over 90 per cent stated they had marked or moderate relief. The onset of pain relief, however, occurs almost twice as rapidly when Nisentil is used. The average duration of analgesia for a single dose is approximately 70 per cent as long as for meperidine. Because of the shorter duration of action of Nisentil, the patients in the group receiving this drug required an average of 1.2 more doses than the patients in the meperidine group.

TABLE II

	NISENTIL		MEPERIDINE	
No. of cases	239		239	
Size of dose	NO.	%	NO.	%
	30 mg. 16	6.8	50 mg. 12	5.2
	40 mg. 215	89.8	75 mg. 37	15.5
	60 mg. 8	3.4	100 mg. 190	79.3
Total no. of doses	1,229		936	
Average no. of doses per patient	5.1		3.9	
Average onset of analgesia	11.9 min.		19.4 min.	
Average duration of analgesia	2 hr., 50 min.		4 hr., 7 min.	
Effect of medication	NO.	%	NO.	%
Marked	131	54.8	120	50.3
Moderate	90	37.6	104	43.5
Slight	14	5.9	13	5.3
None	4	1.7	2	0.9

The same incidence and type of side effects appeared in both groups (Table III). Nausea and/or emesis and diaphoresis were the most common undesirable side effects. While nausea and vomiting occurred with approximately the same frequency in both groups, they were more severe in the meperidine series. In seven patients in this group it was necessary to discontinue the meperidine. Nisentil was stopped in only one instance. Conversely, the diaphoresis caused by Nisentil was more profound, requiring discontinuance of

the drug in six of the twenty-four patients exhibiting this complication. Meperidine did not have to be stopped for this cause. Respiratory depression occurred in three patients in the Nisentil group and in five in the meperidine series. In all but one case the depression was slight and of short duration. One patient receiving meperidine required oxygen by mask for one hour. N-allylnormorphine was not required in any case of respiratory depression.

TABLE III

SIDE EFFECTS	NISENTIL		MEPERIDINE	
	NO.	%	NO.	%
Nausea	35	14.6	37	15.5
Vomiting	9	3.6	12	5.2
Diaphoresis	24	10.4	17	7.2
Respiratory depression	3	1.2	5	2.1
Weakness	5	2.1	9	3.6
Headache	4	1.7	2	0.9
Mental confusion	1	0.4	1	0.4
Dizziness	1	0.4	4	1.7
Pruritus	3	1.2	2	0.9

The subjective effects on patients receiving Nisentil were generally good. No patient complained of having to receive injections every two hours, and many patients were pleased that they were getting medication for pain at frequent intervals. Most patients experienced a sense of well-being when their pain was relieved. The major complaints came from those individuals who experienced profuse diaphoresis from Nisentil. In six cases it was necessary to discontinue the medication because of excessive perspiration despite adequate pain relief in five of these patients.

DISCUSSION

The search for new analgesic agents as satisfactory substitutes for morphine has progressed rapidly in recent years, but, as Batterman and Oshlag[13] emphasized, we are not really looking for a substitute for morphine but rather an analgesic which will be superior to it. Most drugs used for analgesia have proved their value except for the unfortunate side effects.[14] Addiction, respiratory depression, nausea, and vomiting produced with morphine usage unfortunately have also been reproduced with many of the newer analgesic drugs.[15]

In addition, we have noted that in certain surgical procedures which are of long duration and necessarily traumatic, as in orthopedic surgery, there is some degree of circulatory depression postoperatively. The patient receives a dose of morphine or meperidine for pain relief and promptly there follows a profound vascular depression. Van Dyke[15] stated that this hypotensive action observed with morphine, meperidine, or methadon is caused by a direct action on the vascular musculature. Clinically we did not reproduce this effect in using Nisentil in our series.

Experimentally, this circulatory effect was produced in animals only with doses of Nisentil exceeding those recommended in human therapy.[16]

It may also be true, as Beecher stated,[17] that existing pain plus its associated psychic modifications is the stimulus and that the euphoria-producing action of morphine may be responsible for most of its pain-relieving properties. Nevertheless, the associated pain pathways in the delicately adjusted autonomic nervous system which may have become disturbed by surgery are proof of pain perception.[18]

We also agree with Batterman[19] that the patient's description and complaint are our sole guides and should be accepted regardless of the type of surgery and/or his mental make-up. The use of noneuphoric drugs which produce apparent complete relief should supply ample proof of their effectiveness.

Here, the drug Nisentil was found to be an effective analgesic postoperatively with comparatively few undesirable side effects. There was little hypnotic effect noted and many of the nurses reported that after the pain was relieved quickly the patients were often sleepless. A synergistic accumulation with anesthetic agents still present in the patient apparently did not result.

Since subjective responses were essential for evaluation of the effectiveness and any side effects of Nisentil, a conscious and cooperative patient was a main consideration. All types of patients tolerated Nisentil quite well and most of them were in complete possession of their sensory responses. They almost all agreed that the drug which had been administered for relief of pain had acted rapidly and adequately. They also attested that the analgesic action was of short duration, particularly those who may have had other analgesic agents prior to this event. Psychologically however, this short duration may be of benefit in that the "injection" may be repeated in two hours instead of the customary "q. 4 h."

In terms of its analgesic potency, Nisentil appeared to be less likely to produce sedation, mental dullness, nausea, and vomiting than did meperidine. Since euphoria was not a striking response it would presumably not facilitate habituation. However, it is too early to state whether or not it will result in primary addiction with extended clinical use.

SUMMARY

Nisentil and meperidine were administered subcutaneously to 478 patients for the relief of postoperative pain. There were 239 patients in each group. Dosages of Nisentil varied from 30 to 60 mg. given every two hours as required. Meperidine in 50 to 100 mg. doses was given every four hours as required.

The average number of doses of Nisentil per patient was 5.1 as compared with 3.9 for meperidine.

The onset of pain relief with Nisentil occurred in 11.9 minutes; with meperidine in 19.4 minutes.

Analgesia was obtained for an average of two hours and fifty minutes with Nisentil and four hours and seven minutes with meperidine.

Nausea and emesis occurred slightly less frequently with Nisentil and were more severe with meperidine. Diaphoresis was observed more often with Nisentil and was more profuse than with meperidine.

CONCLUSION

1. Nisentil, a synthetic piperidine derivative, in 30 to 60 mg. doses compares favorably with meperidine as an analgesic.

2. The onset of action is rapid and the duration relatively brief, which may be a psychologic advantage.

3. Nisentil is well tolerated by most patients and its rapid onset of pain-relieving action is appreciated by all patients.

4. Its lack of euphoric effect and mental dullness makes for an improvement over previously used analgesic agents, particularly with respect to addiction.

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AXIAL ENTEROENTEROSTOMY BY A TELESCOPIC CUFF METHOD USING A SINGLE ROW OF CONTINUOUS SUTURES: AN EXPERIMENTAL STUDY

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THIS is a discussion of a new and relatively unknown technique for bowel anastomosis. Our purpose in these investigations is to explore the possibilities with respect to safety, speed, and functional efficiency of a one-row-suture, telescoping anastomosis whereby one end of the resected intestine is invaginated into the other, after cuffs are prepared on the proximal and distal ends.

Surgeons are in general agreement that: (1) end-to-end intestinal anastomosis is more physiologic, of greater strength, and quicker in performance than lateral anastomosis; (2) intestinal content is septic, and gross soiling must be prevented, but there is remarkable ability of the peritoneum to resist minimal soiling; (3) fibrin which forms in response to injury of the peritoneum rapidly seals off needle holes, and the line of suture, hence the serosa, should be inverted to bring the peritoneal layers in contact; (4) the selection of fine suture material and needles and the choice of suitable suture techniques are important; (5) whatever suture method is used, the sutures must be anchored in the tough submucosa of the gut to be secure; (6) sutures must not be drawn too tightly or necrosis of the wall of the bowel may result; (7) an occasional unintentional penetration of the mucosa may take place, and therefore a second inverting row of sutures is introduced by many surgeons for added security; (8) preservation of an adequate blood supply to the cut ends of the intestine is essential for healing.

The use of special clamps and suture techniques for anastomosis by the so-called "aseptic" method is controversial. Many believe that crushing the bowel tends to squeeze bacteria through the intestinal wall and that only relative asepsis is obtained anyway; also that greater inversion of the margins occurs than by the open suture technique, producing a larger diaphragm. The advent of preoperative intestinal preparation with antibiotics and sulfa drugs has done much to reduce the danger from peritonitis. The trend at present is away from the aseptic or closed type of anastomosis and in favor of the open suture method.

Holman and Connally,[5] in a report on technical improvements in intestinal anastomosis based on experimental observations, concluded (1) that complete reliance could be placed upon a single row of interrupted silk sutures and (2) that interrupted sutures prevented the ringlike purse-string effects of continuous sutures.

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Our method represents a combination and modification of the procedures now to be described.

In 1926, Babcock[1] described a partial gastrectomy by means of a telescoping anastomosis. In brief, he divided the stomach proximal to the pylorus, excised a cuff of gastric mucosa, and sutured the cut edge of the duodenum to this cuff of stomach mucosa thus formed, by a continuous suture. Following this, he sutured the edge of the divided muscular coat of the stomach distally to the seromuscular coat of the duodenum. In 1923 and 1927 Goepel[3, 4] reported the successful use of a similar technique and disputed Babcock's claim to priority.

Seton Pringle[6] described a method of telescopic anastomosis in 1945 as follows: After section of the bowel, proximal male and distal female components were prepared. The mesentery was detached for 2.5 cm. from the male component and three traction sutures were passed into the lumen of the female component 2.5 cm. from the cut end and made to catch the edges of the male component, which was then drawn into the female component, and the sutures which effected the indrawing were tied and cut. The anastomosis was completed with interrupted cotton stitches introduced around the circumference of the invaginated segments and the flaps of the mesentery reunited. According to Bailey,[2] this operation was originated and used successfully by Wright, a veterinary surgeon, before Seton Pringle applied it to man.

EXPERIMENTAL METHOD

Healthy dogs of 10 to 15 kilograms in weight were used. Under pentobarbital sodium anesthesia and strict aseptic precautions a right rectus incision was made and a loop of intestine, either jejunum, ileum, or colon, was drawn out of the abdomen and carefully packed from the peritoneal cavity with moist saline sponges. (Fig. 1.) The mesentery was divided preserving an adequate blood supply to the cut ends, and the intestine was then sectioned. Leakage of bowel content was prevented by intestinal forceps applied proximally and distally to the line of section. A Wassermann tube was inserted into the lumen of the intestine on the proximal side as a temporary support, and an annular seromuscular cuff 0.25 inch to 0.5 inch (8 to 12 mm.) in length was removed by sharp dissection. On the distal side the intestinal mucosa was removed down to the submucosa with dissecting scissors for a corresponding distance. A traction suture of silk on double straight intestinal needles was introduced through the mucosal edges of the proximal bowel segment and then passed distally into the lumen of the distal bowel segment and through its wall, as shown in Fig. 1. The proximal segment could then be invaginated into the distal segment by gentle traction and maintained there while a single circular row of continuous 000 silk suture (Cushing) was introduced, the suture being started at the mesenteric triangle with a mattress stitch and continued around the periphery, suturing the seromuscular coats together. The traction sutures were then withdrawn, the mesentery reunited, the intestines replaced in the abdomen, and the wound closed in layers with silk.

Other than the omission of food on the morning of operation, no special preoperative bowel preparation was instituted and neither sulfa drugs nor antibiotics were given pre- or postoperatively. In all, the procedure was performed on eleven animals with one death, the cause of which was not clear.

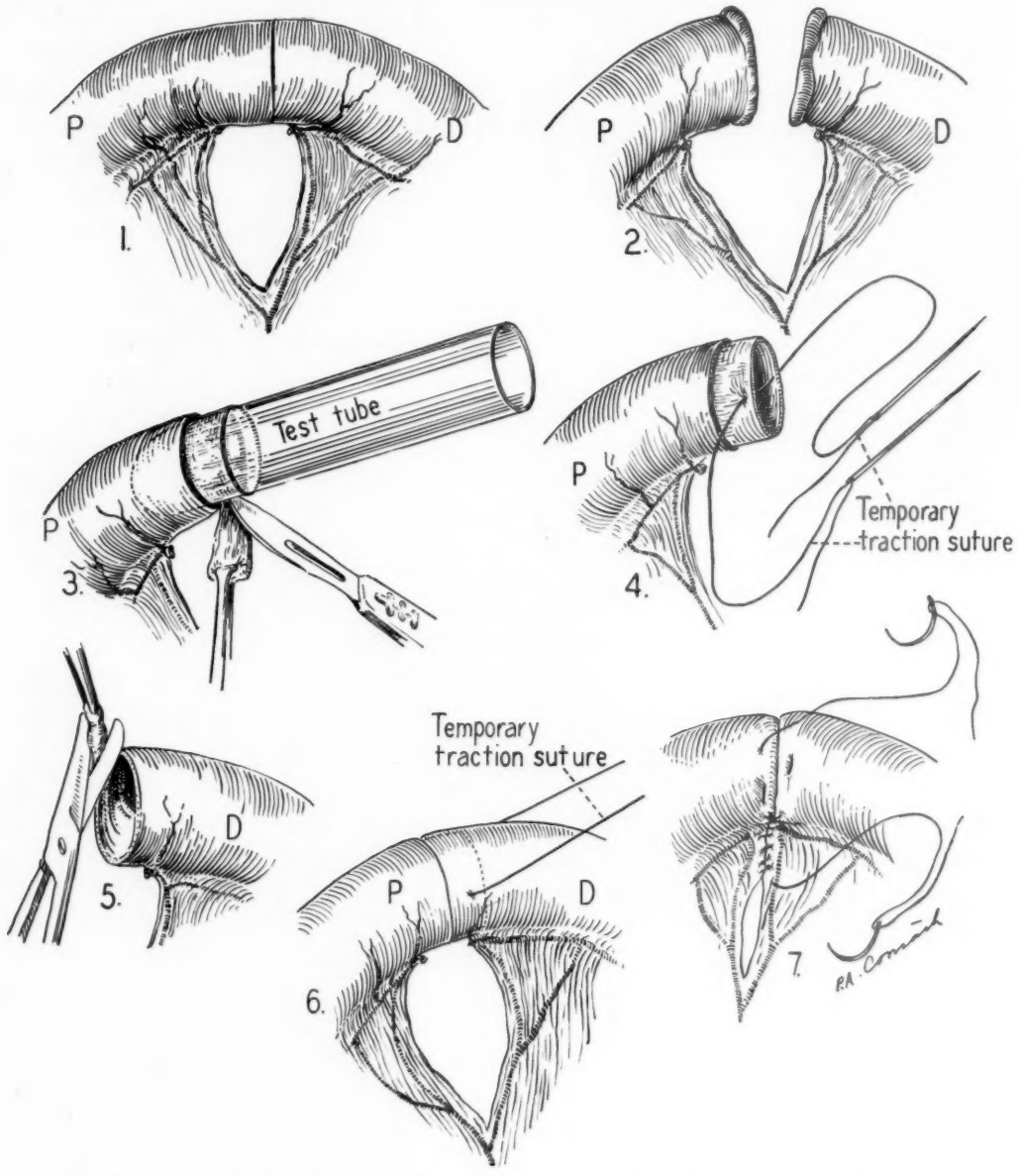

Fig. 1.—Operative technique. *1*, Division and removal of mesentery on proximal side of the line of section; first stage in preparation of the cuff. *2*, Bowel sectioned. *3*, Small glass tube inserted in lumen as a temporary support to aid in the quick removal of an annular seromuscular cuff. *4*, Introduction of temporary traction suture. *5*, Excision of a mucosal cuff on distal component. *6*, Invagination of the proximal into distal component. *7*, Continuous mattress suture.

EXPERIMENTAL RESULTS

Dog No. 1, male, 18 pounds: An axial telescopic cuff anastomosis of the colon was performed as described previously. The animal was killed after six

weeks. The postoperative course had been uneventful. The line of anastomosis on the serosa was scarcely visible. The segment was removed and opened longitudinally for gross inspection of the anastomosis. There was a moderate inverted flange of mucosa. A section was removed and stained with hematoxylin and eosin for histologic study. All layers were completely healed. (Fig. 2.)

Fig. 2.—Photomicrograph of anastomosis; healing of the muscular and mucosal coats is evident.

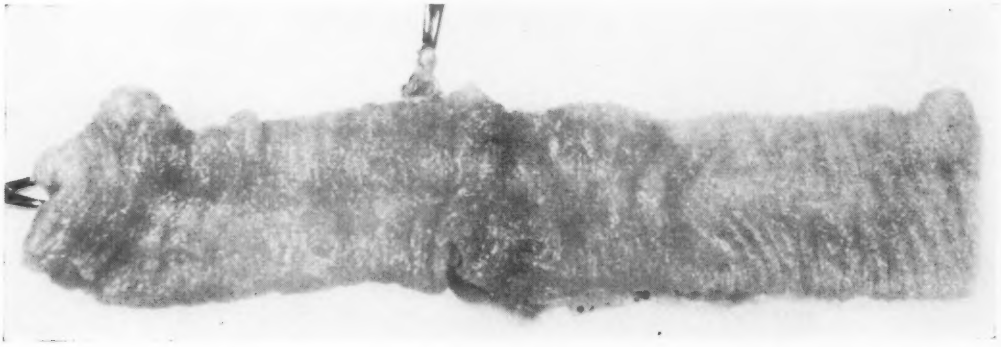

Fig. 3.—Photograph of mucosal side of the opened gross specimen. The line of anastomosis is shown by the elevated fold of mucous membrane.

Dog No. 2, male, 20 pounds: Telescopic cuff anastomosis of the colon was performed. This animal was reoperated on after six weeks. He had been in a state of excellent nutrition. The loop containing the intestinal anastomosis was excised. There was moderate stenosis at the site of anastomosis. Histologic study showed complete healing of all coats.

Dog No. 3, male, 30 pounds: Telescopic cuff anastomosis of the jejunum was performed. The postoperative course was uneventful with no loss of weight. The animal was killed after thirty-eight days. On gross inspection there was normal healing of the anastomosis. (Fig. 3.) The loop of intestine containing

the anastomosis was removed, filled with barium, and an x-ray film made. (Fig. 4.) Constriction of the lumen was approximately 50 per cent. Sections stained with hematoxylin and eosin showed normal healing of all coats.

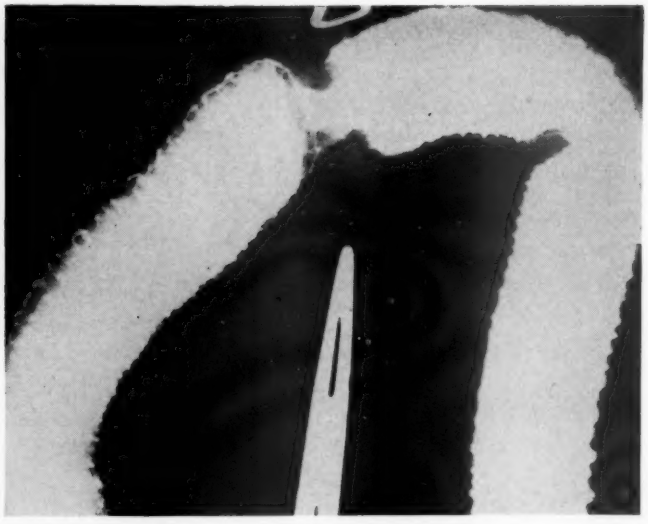

Fig. 4.—Barium-filled loop of jejunum; the site of anastomosis shows a constriction of approximately 50 per cent; there is no dilatation of the proximal loop.

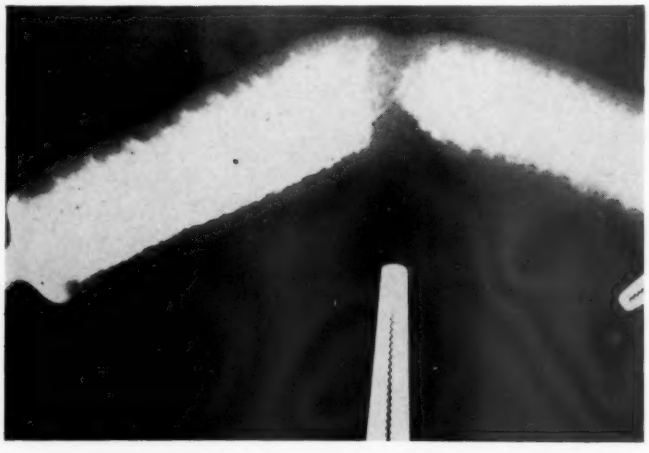

Fig. 5.—Barium-filled loop of jejunum showing constriction at site of anastomosis approximately 50 per cent—no dilatation of the proximal loop.

Dog No. 4, male, 35 pounds: An axial telescopic cuff anastomosis of the jejunum was performed. The animal seemed in good health, the bowels moved regularly, and there was no loss of weight. After three weeks he was killed. The gross specimen showed minimal peri-intestinal adhesions. There was a slight degree of stenosis at the anastomotic site. Sections stained with hematoxylin and eosin showed normal healing of all coats.

Dog No. 5, male, 30 pounds: An axial telescopic cuff anastomosis of the jejunum was performed. The postoperative course was uneventful. The dog was killed three weeks later. Sections made through the line of anastomosis and stained with hematoxylin and eosin showed normal healing of all coats. An x-ray film (Fig. 5) of the barium-filled segment shows constriction of the lumen at the line of anastomosis of approximately 50 per cent.

Dog No. 6, male, 35 pounds: An axial telescopic anastomosis of the jejunum was performed. Six months later the animal was killed and the anastomosis inspected. It was found to be completely healed. An x-ray film (Fig. 6) with the lumen filled with barium shows only slight constriction, approximately 20 per cent.

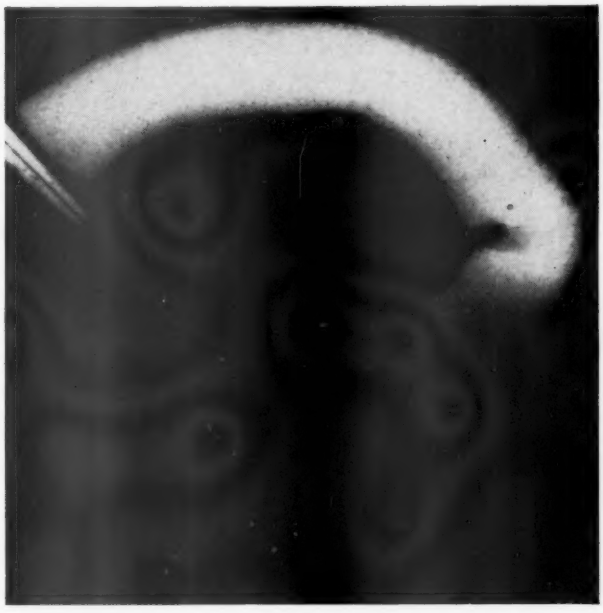

Fig. 6.—Barium-filled loop of jejunum showing an anastomotic constriction of approximately 20 per cent.

Dog No. 7, male, 30 pounds: A jejunal telescopic axial anastomosis was performed. The animal was killed five months later. Section stained with hematoxylin and eosin showed normal healing and x-ray film of the barium-filled loop revealed only moderate constriction of the anastomosis.

Dog No. 8, female, 17 pounds: A telescopic axial anastomosis of the terminal ileum was performed. The animal was killed after four months, during which she was in excellent health. The anastomosis was completely healed and constriction at the site of anastomosis was minimal.

Dog No. 9, female, 17 pounds: An axial telescopic anastomosis of the colon was performed. During operation there was gross peritoneal soiling with feces. The animal remained in perfect health, had a good appetite, and regular bowel movements. She was killed six weeks later and the anastomosis examined. Fig.

7 is an x-ray film of the barium-filled loop. Measurement at the site of anastomosis indicates a 50 per cent reduction of the lumen.

Dog No. 10, male, 25 pounds: A telescopic anastomosis in the upper jejunum was performed. The animal was killed after five months. He had been in excellent health. The anastomosis was completely united; there were minimal adhesions and minimal constriction of the lumen.

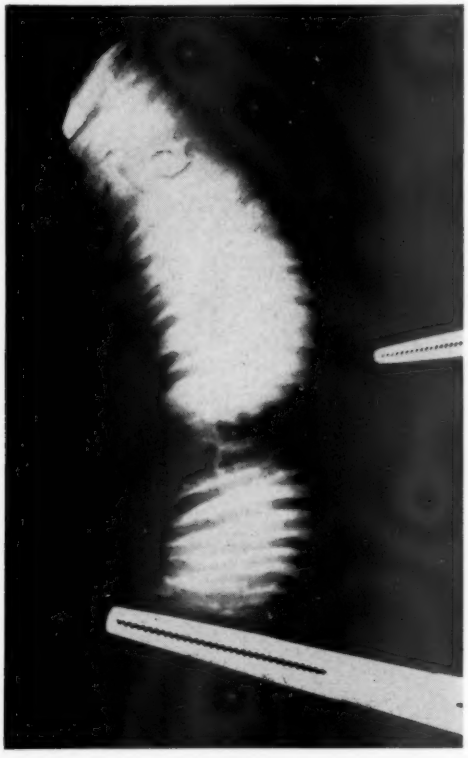

Fig. 7.—Barium-filled loop of colon showing approximately 50 per cent constriction at site of inversion with no dilatation of proximal loop.

Dog No. 11, male, 18 pounds: A telescopic cuff anastomosis of the ileum was performed. The animal appeared to be doing well but died suddenly on the thirteenth postoperative day. There were extensive adhesions but no bowel obstruction. There was no general or localized peritonitis. An x-ray film of the barium-filled segment showed narrowing of the lumen of approximately 40 per cent. Sections stained with hematoxylin and eosin showed healing progressing normally.

COMMENT

A method of anastomosis of small intestine and colon is described based on the principle of telescoping the proximal segment of the gut into the distal segment after preparation of suitable cuffs. The procedure, while similar, differs from Goepel's, Babcock's and Seton Pringle's operations in several respects: (1) It may be applied to the small intestine, whereas in Goepel's

and Babcock's stomach operations, suture of the mucosal edges would be impractical in the small intestine. (2) The areas in contact for healing are the two submucosal layers and not the serosal and mucosal coats as in the Wright-Pringle operation. (3) A more uniform adaptation of the proximal and distal segments results when a cuff is formed and, theoretically at least, the lumen should not be encroached on to the same extent as when the entire thickness of the intestine is utilized, as in the Wright-Pringle operation. (4) The mucosal edge is not exposed on the peritoneal surface; this would seem to minimize local infection with subsequent occurrence of troublesome adhesions. (5) The traction sutures are removed after the anastomosis is completed, eliminating the possibilities of leakage along the suture tracts.

The operating time was materially reduced when compared to that required for end-to-end anastomosis by the standard two-row suture method, and stenosis at the site of union, as determined by post-mortem x-ray films of the barium-filled intestinal loops, was no greater than with the two-row-suture technique. There were no deaths from peritonitis, no postoperative bleeding from the unsutured mucosal edges, and no instance of bowel obstruction. The animals remained in excellent health, had good appetites and regular bowel movements, and maintained their body weight during the varying periods of observation. There was one death, Dog No. 11, the cause of which was not clear.

One disadvantage, however, is an inverted flange of the mucosa which encroaches upon the lumen. This in our experience varied from 20 to 50 per cent and appears to depend on the length of the prepared cuff. We began making shorter cuffs after x-ray visualization revealed the size of the inverted flange in our earlier experiments. It may be, as Holman and Connally contended, that interrupted sutures cause less purse-string effect than continuous sutures. Clinically we could see no difference in the behavior of the animals. It is believed that the intraluminal pressure exerted against the mucosal cuff acts as a barrier and protects the suture line against leakage.

The method might well be of interest to physiologists and experimental surgeons where speed and simplicity, consistent with safety, are desired. With more experience it is possible that this or some similar one-row suture technique may prove of value in civil or military surgery, particularly in instances requring multiple bowel resection.

CONCLUSIONS

Axial enteroenterostomy may be successfully performed by telescoping the ends of the intestine after preparing cuffs denuded proximally of the seromuscular layer and distally of the mucosal layer and uniting them by a single continuous stitch. This is a safe, simple, and rapid method and provides an anastomosis with no more constriction of the anastomotic ring than one might expect with the conventional two-row axial suture technique or with the use of so-called "aseptic" intestinal clamps. We believe

that further investigation of a comparative nature might be undertaken to determine which of several single-suture end-to-end procedures is most effective.

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X-RAY VISUALIZATION OF SURGICAL SPONGES

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DESPITE elaborate precautions and procedures aimed at the prevention of leaving surgical sponges in patients after operations, this unfortunate event continues to occur, undoubtedly with much greater frequency than is reported in the literature. Various interesting accounts of such occurrences have been published, many with relatively minor consequences and replete with bizarre chains of events and symptomatology, and quite a few with patient fatalities and sometimes catastrophic consequences to the responsible surgeon.[1, 2] The excellent reference work of the Crossens[3] should be read by all who are interested in the general subject of foreign bodies left in the abdomen. More than thirty years ago it was reported that in a period of five years at the Mayo Clinic thirteen operations were performed for the removal of gauze foreign bodies.[4] While it has been demonstrated that it is possible to locate and identify plain all-gauze sponges in the abdomen without special x-ray detectable telltales, this is technically difficult and depends upon the visualization of shadows of air entrapped in the sponge,[5] or of calcification if and when it occurs.

Since there is no presently available absolutely certain means of preventing the overlooking of sponges, it would seem that probably the best approach to the problem combines the constant vigilance of the surgeon in following whatever method of prevention is best adapted to his circumstances and, in addition, the use of materials which will minimize the consequences when some unanticipated chain of circumstances does result in the loss of a sponge. This report concerns such materials.

For about ten years sponges have been generally available which contain x-ray-detectable materials and are thus capable of being identified and accurately located within the body. It has been well established that the use of these sponges provides a very desirable safeguard in that when it is suspected that a sponge has been left inside a patient, it is possible to determine promptly whether or not this is the case, without recourse to an exploratory surgical procedure. When the roentgenogram does verify the presence of the radiopaque component of the sponge, its position may be accurately determined, and the risk attending its removal is thus lessened. Recently Etter and Rice[6] have emphasized the importance of the survey radiograph of the abdomen in surgery.

These x-ray-detectable sponges have received widespread acceptance in teaching hospitals in this country, and at the present time those which are most commonly used have barium sulfate-treated inserts.

Grateful acknowledgment is made of the participation of members of the Departments of Anatomy and Radiology of the Jefferson Medical College of Philadelphia.

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Recently theoretical considerations in the field of physical chemistry indicated that a possible improvement might be made by using lead silicate instead of barium sulfate. It was postulated that the heavier atomic weight of lead as compared with barium might make it possible to achieve an equal or greater degree of visualization with a smaller filamentous diameter.[7] The use of lead glass thread for this purpose had been studied and recommended several years ago.[8] Pharmacologic studies had demonstrated lead silicate to be chemically inert and not vulnerable to attack by enzymes and chemical substances in the body fluids.[9]

It seemed desirable to attempt to obtain a comparison of the lead glass thread material with the presently used barium sulfate monofilament telltales under conditions which would closely simulate those of actual clinical usage. Accordingly, experimental sponges were prepared, each of which contained a lead glass thread consisting of sixteen monofilaments woven into a single strand and encased in an inert and extremely resistant plastic film sheath. The diameter of the lead glass thread was 0.008 inch as compared with the 0.017 inch diameter of the barium sulfate-coated monofilament. Calculations indicated that the amount of x-ray absorption would, at 70 kilovolts, be about the same in the two materials.

A second objective was not envisioned until an examination of the available literature made it clearly apparent that very little work had been published which pertained to the actual radiologic techniques involved in discovering these materials.[10] This point became emphasized when it was brought to our attention that, in the past, occasional difficulty in producing roentgenograms which satisfactorily delineated these markers had been reported. For this reason it became necessary to set up an experiment within an experiment in order to attempt to determine techniques which could be recommended and used with dependability in identifying and locating surgical sponges bearing x-ray-detectable telltales. Furthermore, it became apparent that the effects of uncontrollable respiratory motion in anesthetized patients also deserved study.

While previous studies had established that a technique involving the use of the Potter-Bucky diaphragm is definitely indicated in radiographing parts of greater than 10 cm. thickness,[11] x-ray equipment of a portable nature such as might be brought in and used in the operating room does not usually permit the usage of more than simple stationary grids in conjunction with intensifying screens.

A brief preliminary series of exposures indicated that, when the factor of motion was excluded, little real difference was apparent in anteroposterior roentgenograms, whether the sponges were placed on the surface of the abdomen and thorax, or were placed within the abdomen or thorax. Then, an experiment was set up in which films were exposed with the sponges placed on the surface of the abdomen of a heavily built (abdomen thickness, 22 cm.; chest thickness, 23 cm.) male cadaver. Conventional x-ray equipment was then used to expose films at a milliamperage of 25 and a tube-film distance of 36 inches.

At the outset, a range of kilovoltages was utilized from 40 through 100 in steps of ten. Exposures were made using intensifying screens alone at the 40-kilovolt level. At the 50-kilovolt level, films were exposed with intensifying screens alone, and with them in conjunction with the Potter-Bucky diaphragm. At the 60-, 70-, 80-, 90-, and 100-kilovolt levels, films were exposed alone (that is, in cardboard holders), with intensifying screens alone, and with intensifying screens and the Potter-Bucky diaphragm.

At each kilovoltage level and with each technique, three films were exposed: one using a time factor which was calculated to approximate the optimum for bone detail, the second with a calculated underexposure of 25 per cent or more, and the third with a calculated overexposure of 25 per cent or more. For example, at the 80-kilovolt level, roentgenograms made with a Potter-Bucky diaphragm and intensifying screens were given a 3.5 seconds' exposure for an intermediate level with a 2.5 seconds' exposure as a calculated underexposure, and with a 4.5 seconds' exposure as a calculated overexposure. At the 70-kilovolt level, films were also exposed with the sponges inserted within the abdominal cavity, on the anterior surface of the chest, and within the thorax. In this group, calculated overexposures and underexposures were also made. In these roentgenograms the x-ray opaque telltales could be satisfactorily visualized in all the series with one exception, which was an underexposure at the 40-kilovolt level in which both an intensifying screen and the Potter-Bucky diaphragm were used.

It was clearly apparent that the barium sulfate-coated monofilaments were more easily visualized than the lead glass thread. This experiment demonstrated that the diameter of the x-ray-detectable strands should not be reduced below a certain minimum regardless of the relative absorption characteristics of different radiopaque substances.

It is, perhaps, of greater general interest that the validity of the premise was established that the visualization of barium sulfate-treated telltales is best in roentgenograms which provide the best visualization of bone detail. It follows that the optimum exposure for bone detail should always be used.

Having obtained this information, it was felt that, with regard to portable x-ray equipment, a further study was indicated in order to examine the behavior of barium sulfate x-ray-detectable materials at a lower milliamperage, with stationary grids, and when placed within the thorax and abdomen. Accordingly, a second series of roentgenograms was made using the same cadaver.

Portable x-ray equipment was used with the milliamperage constantly held to 10, and the tube-film distance 36 inches. Sponges bearing the barium sulfate telltales were wetted, manually crumpled and compressed, and placed within the thorax and the abdomen. Sponges were so placed that their shadows on the film were superimposed upon bone shadow, as well as upon soft-tissue shadow. Six films were exposed through the chest and six through the abdomen at kilovoltage levels of 60, 70, and 80. Again an intermediate exposure was made which was the calculated optimum for bone detail. By varying the time, a deliberate underexposure which was one-half of the intermediate exposure, and deliberate overexposure which was twice the intermediate exposure, were made.

Again the best roentgenograms were made with a technique which was best for bone detail. While the technique involving the use of the Potter-Bucky diaphragm is definitely better than that of stationary grids with intensifying screens, it is felt that the latter is entirely adequate for the purpose of revealing a sponge and is advantageous in that it requires less exposure time.

In searching for sponges, it may be recommended, when stationary grids are used, that the high kilovoltage levels should be employed and that the highest milliamperage level which is available be used. With a milliamperage of 10, it is recommended that a kilovoltage of 80, in conjunction with stationary grids, be used for all adults in order to keep the exposure time short where respiration is uncontrollable.

Fig. 1.—Roentgenogram of chest. Portable equipment with sponges wetted, crumpled, and placed overlying soft-tissue shadows as well as bone shadows. Exposure factors: 10 milliamperes, 80 kilovolts, 4 seconds' time, using intensifying screen and stationary grid.

It should further be pointed out that when intensifying screens are used alone, better roentgenograms are obtained at the 60-kilovolt level than at the 70-, and 80-kilovolt levels for the purpose of sponge detection. However, for both the abdomen and chest, exposures through a stationary grid at 80 kilovolts are both shorter in time and far superior to exposures at 60 kilovolts through an intensifying screen alone. Furthermore, at the kilovoltage levels from 60 to 80, the technique may be varied as to timing by as much as 100 per cent in milliamperage seconds from that regarded as optimum and still produce films on which the telltales are readily discernible.

The effects of respiratory motion were studied by placing sponges containing x-ray-detectable inserts within the thorax or abdominal cavities of three anesthetized patients. Sponges were placed dry and flat, as well as moistened and crumpled, into patients just prior to closure. Portable x-ray equipment was used to expose film through stationary grids which had been placed on the operating table prior to beginning the surgical procedure. Depending upon the size of the patients, exposure times ranged from 2.3 to 3.0 seconds. Respiratory rates varied from 16 to 28 per minute and also varied as to depth.

Fig. 2.—Similar roentgenogram of abdomen with the same factors as in Fig. 1 except that the exposure time was lengthened to 5 seconds.

As would be expected, it was found that the obscuring effect of motion varied in direct relation to the proximity of the sponges to the diaphragm and was more serious in the thorax than in the abdomen. Futhermore, in procedures near the diaphragm, particularly in the thorax, the best roentgenograms made with long exposure times may fail to detect the telltales when the respiratory rate is rapid. Hence, one cannot always place reliance upon roentgenograms made under these circumstances and which fail to show the telltales. Roentgen studies made with conventional x-ray equipment with the cooperation of the patient in holding the breath would be necessary in order to be certain of the absence of a sponge.

CONCLUSIONS

The use of surgical sponges which contain x-ray-detectable inserts represents a desirable factor of additional safety in surgery of the abdomen and thorax.

While the use of conventional x-ray equipment and the Potter-Bucky diaphragm was found to produce the best roentgenographic delineation of these sponges, highly satisfactory roentgenograms are easily obtainable with portable equipment and stationary grids.

Exposure techniques should always be used which would be expected to show the best osseous detail in the area of suspected sponge loss. When using low milliamperage portable equipment, the highest available kilovoltages should be used with stationary grids. The danger of failure of roentgenographic demonstration of telltales due to under- or overexposure is not actually as great as might have been expected.

The adverse obscuring effects of uncontrollable respiratory motion are of greater magnitude in trying to locate sponges in the thorax than in the abdomen. When a negative roentgenogram is obtained with portable equipment under these circumstances, it is recommended that a subsequent final check be made with conventional equipment when the patient can cooperate in holding the breath. Under these circumstances any telltale-bearing sponge which may be present will be easily visualized without fail.

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Case Reports

TRAUMATIC RUPTURE OF BOTH LEAVES OF THE DIAPHRAGM

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TRAUMATIC rupture of one leaf of the diaphragm is not too uncommon a finding in this day of the rapidly moving vehicle; however, the occurrence of a rupture of both leaves of the diaphragm is a rare clinical finding and has not been reported frequently in the literature.[1, 2] Because of the unusual character of the lesion we should like to report the following case.

CASE REPORT

A 6-year-old white boy was struck by a truck on Nov. 25, 1942. He was admitted to Ancker Hospital immediately following, in an unconscious state. After a short period of time, he regained consciousness.

External examination revealed a well-developed, well-nourished, white male child with an extensive laceration of the right arm and a contusion of the skin in the epigastric region of the abdomen. His color was good and he did not appear to be in shock. He was complaining of mild pain in the abdomen which gradually increased in severity, and he was not dyspneic when first admitted.

Examination of the chest was essentially negative to auscultation and percussion. The blood pressure was 120/64 and pulse rate was 120. His respirations soon became labored and he became lethargic. The heart rate was regular and no murmurs were detected. Examination of the abdomen revealed a moderate generalized upper abdominal tenderness, but no muscle rigidity and no rebound tenderness. No abnormal masses were detected in the abdomen. The bowel sounds were normal, and there was no costovertebral angle tenderness. Rectal examination was noncontributory. The neurological examination was essentially within normal limits except for slowly progressing lethargy. The hemoglobin was 12.9 Gm., and urinalysis was essentially normal, there being no microscopic hematuria.

X-ray examination of the chest revealed the lung fields to be clear. There was no evidence of pneumothorax or atelectasis, and no rib fracture could be detected. The left diaphragm was slightly higher than the right and there was an area of increased radiability below the left diaphragm in which no lung markings were seen. There was suggestive evidence of free air beneath the left diaphragm, although this was atypical in appearance. No air was seen between the liver and the right diaphragm. X-ray films of the skull revealed a linear fracture in the right parietal region.

Because of the patient's increasing abdominal pain associated with suggestive free intraperitoneal air, an exploratory laparotomy was performed through a high bilateral subcostal incision. At this time it was found that both domes of the diaphragm had been ruptured. There was no evidence of a retroperitoneal hematoma, and no ruptured solid or hollow viscus was present. The stomach was found to lie partly within the left chest cavity. The rupture of the right leaf of the diaphragm measured approximately 10 cm. in length, while that of the left measured approximately 15 cm. Both tears began about 3 cm. from the esophageal hiatus and extended in a radial fashion anterolaterally. No

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abdominal viscera herniated through the defect in the right diaphragm. When the abdomen was opened the patient automatically developed a bilateral pneumothorax which was easily controlled by the anesthetist who had previously intubated the trachea. The defects in the diaphragm were sutured with interrupted 000 silk mattress sutures, and as the last suture in each side was placed the lung was fully expanded. The chest x-ray films after surgery showed no pneumothorax. The patient's postoperative course was uneventful, and he had a normal recovery.

DISCUSSION

There are several interesting facets to this case which are worthy of mention. The original exploration of the abdomen was performed because of the presumed presence of a ruptured viscus. The roentgenologist who examined the films suggested that although it appeared as if free air was present beneath the diaphragm, it was not the usual picture; rather it appeared as if a localized pocket of air was partially above and below the diaphragm. This did not seem to be in the stomach. The stomach appeared separate from this collection. The abdominal exploration revealed that in all probability it was stomach trapped in the tear of the left leaf of diaphragm. Fluoroscopy may have helped in diagnosing the rupture. Kerley[3] described the invisibility of the injured dome and intermittent twitching movements of the diaphragm which can be seen fluoroscopically.

If the correct diagnosis had been made and exploration for correction of the tear been made by a transthoracic approach, it is probable that the rupture of the right leaf would have been missed. The presence of an idiopathic pneumothorax on the right side would have presented obvious difficulties, that is, etiology and therapy. It has been our feeling for the past few years that repair of diaphragmatic hernias is generally best accomplished by a transabdominal approach. In cases such as this, we believe that if the diagnosis is made, even of unilateral rupture, that an abdominal approach is the desired one. Not only can the repair be made satisfactorily but the remainder of the abdomen can be explored for other injuries. The latter cannot be done adequately through a thoracic approach.

SUMMARY

A case of traumatic bilateral rupture of the leaves of the diaphragm is presented. Successful repair through an abdominal approach was accomplished. Every effort should be made to rule out the possibility of bilateral diaphragmatic tears when the certainty of a unilateral tear is made. An abdominal approach for the repair of the diaphragm will give adequate exposure and, in addition, allow for the exploration of the remaining viscera.

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PORTAL HYPERTENSION ACCOMPANYING CHOLANGITIS DUE TO STRICTURE OF THE COMMON BILE DUCT: CORRECTION BY SPLENORENAL SHUNT

A Case Report

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THE damaging effects on the liver resulting from biliary obstruction have been recognized for many years. The pathologic anatomy of this condition, described by Hanot and termed "biliary cirrhosis," originally included all forms of cirrhosis caused by biliary obstruction. Refinements of this classification have been made on the basis of the site of the obstruction. Hanot's type of cirrhosis is now considered to be that associated with cholangiolitic or intrahepatic obstruction of the fine biliary channels, and termed "primary hypertrophic biliary cirrhosis." The extrahepatic form of obstruction resulting from calculi, neoplasms, and strictures, either traumatic or inflammatory, may cause similar changes in the liver, and is referred to simply as "biliary cirrhosis."[1] Exception has been taken to this classification by some authors, but the merits of this controversy are not within the scope of this paper.

Pathologically, biliary cirrhosis is characterized by dilatation, proliferation, and tortuosity of the biliary channels within the liver. There is some destruction of liver cells and replacement by scar tissue, particularly noticeable in the areas about the portal veins and bile ducts (Fig. 1). The presence of superimposed infection enhances the process. The spleen is usually enlarged, but clinical evidence of portal hypertension is rare, and most authors in discussing this disease attach minimal significance to the probable development of portal hypertension.

This type of cirrhosis has been produced experimentally in animals, including rats, rabbits, cats, and dogs,[3-7] and its similarity to that found in the human being has been noted.[6] Even the rare complication of collateral circulation has been seen in dogs.[7]

Clinical reports of biliary cirrhosis in the human being are plentiful.[8-14] However, as a sequel, portal hypertension is exceedingly rare. In one series of thirty patients, none developed this complication.[8] Autopsy findings in another series of 240 cases of biliary cirrhosis revealed esophageal varices in only two cases.[10] Still another statistical survey of 3,000 autopsies showed the incidence of biliary cirrhosis due to chronic extrahepatic obstruction to be 0.4 per cent, and none of these showed evidence of portal hypertension.[13] Portal obstruction is seen occasionally terminally, when ascites and rarely hematemesis may occur.[15, 16]

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In the recent literature, seven such cases have been reported. In four of these, the site of the biliary obstruction was intrahepatic, within the fine biliary channels.[11] In all four cases, ascites was present, but esophageal varices were found in only two. The remaining three cases resulted from or accompanied extrahepatic biliary obstruction. In two of these, ascites was a clinical feature, but esophageal varices were not evident.[12] In the remaining case, both ascites and varices were present.[14]

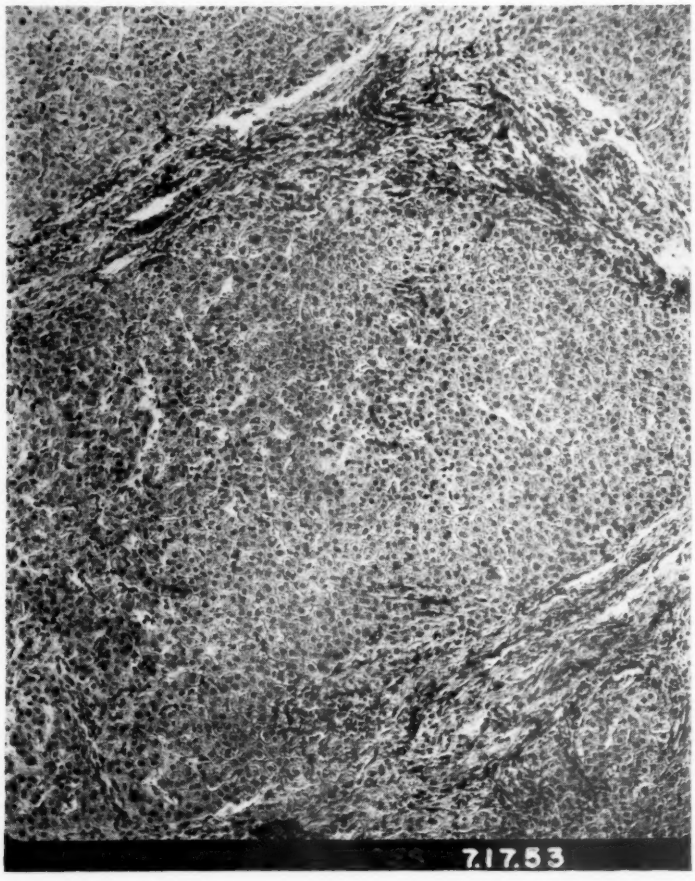

Fig. 1.—Photomicrograph of liver biopsy taken at time of splenorenal shunt, illustrating the fibrosis in the portal areas.

Its rare incidence and the possibility, in certain instances, of portal vein thrombosis as a result of previous operation upon the biliary system make the diagnosis of biliary cirrhosis with portal hypertension extremely difficult.

CASE REPORT

A 40-year-old white woman was admitted to Stanford Hospital for the first time in September, 1949. Seven weeks before entry, a cholecystectomy for cholelithiasis had been performed at another hospital. The common duct was neither explored nor drained. Five days following operation, jaundice appeared, which became progressively severe, and was accompanied by acholic stools, dark urine, nausea, and vomiting, all of which were present on entry. She had lost 25 pounds in weight.

Examination revealed evidence of recent weight loss, and the skin and sclerae were markedly icteric. There was the recently healed scar of a right rectus incision, and the liver extended 5 cm. below the costal margin and was very tender. The temperature was 37.3° C.; the blood pressure was 135/80, pulse 110, and respirations 20. The red cells numbered 3,195,000; hemoglobin was 10.1 Gm.; hematocrit 31; white cells numbered 2,950 with a normal differential. The bleeding, coagulation, and prothrombin times were normal. The icterus index was 175. The urine contained bile, but was otherwise normal, and the stools were acholic.

Two days after admission an exploration was performed through a right, abdominothoracic incision. A large, firm, greenish, discolored liver was separated from the stomach and first portion of the duodenum with difficulty, because of adhesions. The common duct was partially obliterated between a blind pouch distally and a completely sealed off duct system in the hilum of the liver. A reconstruction was performed using a No. 18 mushroom catheter. This was passed in a retrograde manner from the duodenum through the ampulla and distal common duct pouch into the incised duct of the liver bed. The mucosa of the duodenum was sutured to the duct in the liver bed. The catheter was then brought out through a separate stab wound. A biopsy of the liver was performed which microscopically showed chronic obstructive cholangitis. The patient ran a febrile course for four days, followed by steady improvement. On the eleventh postoperative day the icterus index was 100. She was discharged from the hospital with the catheter in place on the twentieth postoperative day.

The catheter was removed one month later, at which time the icterus index was 75 and the stool was positive for bile. However, within three weeks, the patient noticed a recurrence of the jaundice and acholic stools. She was readmitted to the hospital in January, 1950.

The icterus index had risen to 100, the stools were acholic, and it was evident that she was again obstructed. A second reconstruction of the common duct was performed by anastomosing the duodenum to the hepatic bile ducts at the bifurcation. A No. 16 catheter was used. Postoperatively, the patient improved steadily and was discharged from the hospital three weeks later. Additional studies during this admission revealed a total protein of 6.4 Gm. per cent, with a 1.67 albumin-globulin ratio, negative cephalin flocculation, and a normal prothrombin time.

The catheter was removed three months following surgery, and the patient did well until June, 1950, when she developed a urinary tract infection. This condition was treated successfully with Aureomycin. However, following this episode she noticed a return of the jaundice, acholic stools, and severe pruritis.

Two days prior to the next hospital entry in July, 1950, the patient passed several tarry stools, and eight hours before admission had a severe episode of hematemesis. On admission, the following laboratory data were obtained: red blood cells 3,010,000; hemoglobin 10.9 Gm.; white cells 14,250; icterus index 40; prothrombin time normal. She had received a transfusion of 500 c.c. of whole blood before admission. She continued to vomit blood and required 4,500 c.c. additional whole blood before surgery. Pertinent studies during hospitalization revealed large esophageal varices (Fig. 2); a cephalin flocculation of 3 plus; Bromsulphalein retention of 36 per cent in forty-five minutes; and van den Bergh direct reaction of 1.2 mg. per cent, total 4.8 mg. per cent. She had also developed a moderate degree of ascites.

The diagnosis of cirrhosis with portal hypertension was made, and in August, 1950, an anastomosis was made between the splenic vein and the left renal vein following splenectomy. The measured portal pressures were 49 cm. water before shunting and 26 cm. water after surgery. Her postoperative course was very satisfactory. The patient was discharged two weeks following surgery with an icterus index of 18.

The patient was essentially well for the next nine months. At no time were the stools melanotic, and the ascites disappeared. She had gained 30 pounds in weight. Four

weeks before her next entry she began to develop severe jaundice, acholic stools, severe pruritis, and nausea without vomiting. On admission in June, 1951, she was markedly icteric, the liver was again 4 cm. below the costal margin and very tender. Laboratory studies revealed an icterus index of 150; direct van den Bergh 2.4 mg. per cent, total 13.0 mg. per cent; normal prothrombin time; Coombs' test negative; cholesterol 287 mg. per cent; phosphorus 3.56 mg. per cent; alkaline phosphatase 21.84 Bodansky units; cephalin flocculation 1 plus; red blood cells 3,600,000; white cells 7,500; hemoglobin 13.6 Gm. Her chief complaint was the severe pruritis, for which she received 50 and 100 mg. of cortisone daily, with prompt relief. During her hospitalization the jaundice began to subside spontaneously, and at the time of her discharge, two weeks later, the stool was positive for bile.

Fig. 2.—Roentgenogram of lower esophagus illustrating esophageal varices outlined by barium contrast medium.

During the next nine months the patient was again essentially well, only to have another episode of jaundice, slightly less severe than the previous one. This subsided spontaneously, but in August, 1952, jaundice recurred for which she was hospitalized. On entry, physical examination was essentially unchanged from that previously noted in June, 1951. The icterus index was 175. A third reconstruction of the common duct was performed through a Kehr incision.[17] The previous anastomosis was taken down and a Roux-Y hepaticojejunostomy, jejunojejunostomy was performed using a No. 18 catheter through the anastomosis of jejunum and liver hilus. The patient's postoperative course was uneventful, and she was discharged on the fourteenth postoperative day feeling well. The catheter was removed two months following surgery.

The patient has remained well to the time of this report. She is no longer jaundiced, eats any food without discomfort, maintains a constant weight, and is leading a normal life.

DISCUSSION

In the case presented, the primary problem was correction of the biliary obstruction. It was following the second reconstruction that the clinical features of portal hypertension appeared and surgical intervention became mandatory. The decision as to which shunting procedure was applicable in this case was dictated by two factors. The first was technical in nature. The scarring subsequent to three surgical procedures in the region of the portal system precluded an Eck fistula. The second factor was the recognition of the usual splenic enlargement in such cases. It has been known that approximately 30 per cent of the portal blood flow comes from the splenic vein; hence it was felt that a splenorenal shunt would more likely enhance the end result. The clinical success of the procedure justified its choice.

The necessity for a third common duct reconstruction was unfortunate, but recompensable by the patient's return to normal health.

SUMMARY

The term "biliary cirrhosis," as used in this paper, is described as a form of cirrhosis of the liver caused by extrahepatic biliary obstruction. Pathologically, there is dilatation, proliferation, and tortuosity of the liver biliary channels, some destruction of liver cells, and replacement by scar tissue.

A brief review of the literature is made, noting the experimental production of biliary cirrhosis in many species of animals, its low incidence in man, and the extremely rare complication of portal hypertension and its sequelae, ascites and esophageal varices.

A case report from this hospital is presented describing the sequence of events leading to the onset of biliary cirrhosis, its subsequent complications, and their successful treatment. The patient was initially treated for cholelithiasis by cholecystectomy, followed almost immediately by progressive jaundice. Two reconstructions of the common bile duct were performed, seven weeks and six months, respectively, following the primary surgery.

Six months after the second reconstruction, the patient developed ascites and esophageal varices followed by massive hematemesis. X-ray studies confirmed the presence of esophageal varices, and a splenorenal venous shunt was performed. Clinical improvement followed, but nine months later biliary obstruction again occurred, requiring a third reconstruction: a Roux-Y hepaticojejunostomy and jejunojejunostomy. At the present time, two years after the last operation, the patient is free of symptoms referable to portal and common duct obstruction.

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MASSIVE TRANSFUSION IN THE SEVERELY WOUNDED

Report of a Patient Receiving 23,350 C.C. of Blood in the First Twenty-Four Hours

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THE experiences of World War II pointed out the value of whole blood in the management of the severely wounded. During the Korean conflict, it became apparent that large amounts of blood should be administered to the battle casualty. Replacement of an amount equal to twice the blood volume was not uncommon. As time went on, reports came from various hospitals of the tremendous amounts of blood given to some casualties. The patient herein reported received 23,350 c.c. of type O, low-titer blood in the first twenty-four hours after injury.

CASE REPORT

A 22-year-old American airman was injured by mortar shell fragments on June 26, 1953, at 11:45 A.M. He sustained a penetrating wound of the right upper quadrant of the abdomen and a perforating wound of the left hip and right leg. He arrived at the clearing station twenty minutes after injury. At that time his blood pressure was 0/0 and he was cold, clammy, and semiconscious. Blood transfusion was started ten minutes later, and in the next thirty minutes, 1,700 c.c. of blood was administered. The patient's color improved; he became responsive; and a blood pressure of 130/? was obtained. He was then moved to the surgical hospital by ambulance, arriving two hours and forty minutes after injury.

Upon admission, his blood pressure was 140/80 and his pulse rate 120. Thirty minutes after admission, 1,000 c.c. additional blood had been administered through a cannula in the left leg, but his blood pressure fell to 90/48, pulse rate 142, respirations 42. Transfusion was continued during the time roentgenograms were taken. There was a metallic fragment in the right lower quadrant at the level of the first sacral vertebra. There was an open fracture of the body of the left ilium, with metallic fragments lying lateral to the greater trochanter, and an open fracture of the upper portion of the right tibia.

A catheter was inserted into the bladder and the urine was found to be clear. Since there was a fall in blood pressure and a pulse rate of 160, in spite of the infusion of blood, it was believed that there was continued intra-abdominal hemorrhage. There was progressive rigidity and distention of the abdomen. An additional cannula was inserted into a vein in the left arm since vena cava injury was suspected. The patient was taken to surgery four hours and forty-five minutes after injury. He had received 5,700 c.c. of blood at this time, but his blood pressure was 66/0.

After Pentothal induction and endotracheal ether anesthesia, an exploratory laparotomy was performed through a right rectus incision. Upon incision of the bulging peritoneum, approximately 3,000 c.c. of blood was found. The abdomen was rapidly explored, beginning with the iliac region. Pressure was then placed in the region of the celiac axis and the entire area was observed for bleeding points. A seven-inch, through-and-through

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tear of the inferior half of the right lobe of the liver was bleeding. A gauze pack was inserted, and it appeared that the hemorrhage was under control. Until 2,000 c.c. additional blood was administered under pressure, further surgery was withheld. The patient's blood pressure rose to 100/64, and his pulse rate was 120. Although Gelfoam was placed in the laceration of the liver, bleeding did not cease. Chromic catgut sutures (No. 1) on round, curved needles were placed widely, through and through the liver, to pull the laceration against the Gelfoam pack. Finally hemorrhage was controlled by placing two figure-of-eight sutures with Gelfoam under the sutures on the anterior and posterior aspects of the liver.

The abdomen was explored thoroughly, and no further intraperitoneal damage was observed. The cecum and ascending colon were reflected medially, and the missile tract in the right psoas muscle was located. The muscle was débrided; a 2 cm.-square metallic fragment was removed, and the bleeding points were ligated. Four drains were placed about the liver and brought out through a stab wound in the right flank. Two large drains were placed in the retroperitoneal area, around the damaged psoas muscle, and brought out through a separate stab wound. A final examination showed that bleeding was under control. The abdominal wall was closed in layers. The wound of entrance to the abdomen and wounds of the extremities were débrided. During the operation, which lasted one hour and fifteen minutes, the blood pressure was around 100/60 for approximately one-half of the time, and it went as low as 60/0 at other times. During the operation the patient received a total of 4,500 c.c. of blood, making a total of 20 pints administered following injury. He left surgery with a blood pressure of 80/60, pulse rate 120, and respiration 40.

For the first few hours postoperatively, the patient's pulse rate increased to 150, and his blood pressure fluctuated between 80 and 100 (systolic) in spite of transfusion of an additional 2,000 c.c. of blood. During the first three hours after surgery, he excreted only 7 c.c. of urine. A great deal of oozing could be seen from the wounds, and considerable loss of blood was occurring through the two drainage sites. Three grams of calcium gluconate was given intravenously with no noticeable effect on the oozing or blood pressure.

Four hours after surgery the patient's pulse continued to be 150, and his blood pressure 90/68. A total of 3,500 c.c. of blood had been administered following operation, making a total of 27 pints since injury. It was believed that this patient continued to ooze from all wound surfaces, possibly from the liver. A secondary exploration was thought advisable because the administration of 875 c.c. of blood each hour did not compensate for the blood loss.

Eleven hours after injury, the patient was again taken to the operating room. His blood pressure was 50/40, and his pulse 130. An intra-arterial transfusion was started in the right femoral artery and blood was also pumped into the arm and leg cannulas. The abdomen was re-entered through the previous incision and a massive amount of blood was found in the peritoneal cavity. The liver laceration was not bleeding. A large amount of blood was seen in the depths of the right psoas muscle wound and retroperitoneal area. No definite bleeding point could be found. A large Gelfoam pack and two five-yard gauze packs were inserted into the retroperitoneal area and the ends brought out through an incision in the right flank. Four drains were again placed around the liver. The abdomen was closed with through-and-through wire sutures. Twelve pints of blood were given during the one-hour operation, three of them into the femoral artery, making a total of 39 pints. During the operation the blood pressure was 60/40 and, after administration of 1 ampule (4 mg.) of norepinephrine, the blood pressure rose to 110/80. With discontinuance of norepinephrine, the patient's pulse was 140 and his blood pressure was 0/0. An additional 4 Gm. of calcium gluconate was given with no discernible effect.

The patient remained on the operating table under the care of the anesthesiologist for some time after the completion of the operation. Oozing continued and it was decided that freshly drawn blood might be of value in stopping it. By 2:00 A.M., 40 pints of blood had been given (1 pint of fresh blood); the patient's pulse was 140, respiration 48, blood pressure 110/70. Vitamin K-1 oxide (100 mg.) was given intravenously and three additional pints of freshly drawn blood was given slowly. It was estimated that the ooz-

ing continued at the rate of approximately 300 c.c. per hour. Following the operation and administration of 43 pints of blood (4 of which were freshly drawn), the urine output was 150 c.c. on the third hour and approximately 70 c.c. per hour thereafter. At this time the patient's general condition appeared to be good.

At 5:00 A.M., the patient experienced an acute gastric distention because of malfunction of an indwelling stomach tube, and respiration increased to over 60 per minute. This was relieved by the introduction of a larger stomach tube and the respiratory rate fell immediately to 40. Between the twenty-fourth and thirtieth postoperative hours he improved remarkedly; he appeared to have stopped bleeding. Blood pressure was 120/40, pulse 120, respiration 40. Output of urine was 60 c.c. per hour. He had received a total of 46 pints of blood (7 pints of freshly drawn blood) and 2,600 c.c. of 5 per cent glucose in water within twenty-four hours following injury.

During the early postoperative period, the patient's course was somewhat stormy. His temperature rose to 103° F. on the first day and slowly fell to normal by the fourth day. He received 1,000,000 units of penicillin every four hours and 1 Gm. of Terramycin every twelve hours intravenously. One-half of the pack was removed on the third postoperative day and the remainder on the fourth day. Although there was a great deal of drainage, there was no bleeding. He was sitting in a chair, eating well, by the tenth postoperative day, at which time he was evacuated to the 25th Station Hospital.

In a follow-up letter from the Osaka Army Hospital in Japan, it was stated that the patient was admitted on the twelfth postoperative day in surprisingly good condition. His hematocrit was 39, total proteins 6.7 Gm., albumin 3.2, globulin 3.5. On the twenty-third postoperative day, secondary closure of soft-tissue wounds of the leg was carried out. By the thirty-seventh postoperative day, he was walking about and felt very well. He had occasional bouts of distention and diarrhea, but it was felt that he was ready for transfer to the United States.

DISCUSSION

This severely wounded patient arrived at the clearing station after a long evacuation by litter jeep, with a blood pressure that was too low to be obtained by the cuff method. After administration of 1,700 c.c. of blood, the patient improved and withstood further evacuation to the surgical hospital. This demonstrates the value of resuscitative measures at the division level. It is wise to delay transportation of a severely wounded man for infusion of resuscitative fluids and thus prepare him for further transport, rather than to rush him to a hospital in extremely poor condition.

Although the patient's blood pressure on admission to the hospital was 140/80, it soon fell to 90/48 in spite of continuous infusion of blood. Failure of the patient to maintain a normal blood pressure and a rapidly expanding abdomen were evidence of profuse hemorrhage intra-abdominally.

Since vena cava injury was suspected, an additional cannula for administration of resuscitative fluids was inserted into an arm vein because leg cannulas are of little value in the presence of such injuries.

An immediate operation was carried out to control hemorrhage. At operation, a large amount of blood came from the damaged retroperitoneal muscles. Blood loss from this area is always much greater than is apparent. After the brisk hemorrhage was controlled by gauze packs, further operation was delayed until additional blood had been given. This illustrates an important point in resuscitation, namely, that when continued profuse intra-abdominal hemorrhage is suspected, immediate exploration is indicated. As soon as

the hemorrhage is controlled, further manipulation should be delayed until the patient's condition is improved by further replacement of blood.

Although continued oozing was obvious after operation, hypotension with the accompanying low output of urine in spite of administration of 876 c.c. of blood per hour was further indication of serious hemorrhage. The second operative procedure was started when the patient was in very poor condition. Blood pressure was 50/0. The patient was reopened under minimal anesthesia, and further restoration with blood was carried out. It is doubtful if the intra-arterial transfusion was of particular value, in this instance, because of the slow rate at which it was given—1,500 c.c. in one hour.

At the first operation, the liver hemorrhage was controlled by large sutures over Gelfoam. Bleeding was from multiple points in the damaged retroperitoneal muscle. It is not uncommon for oozing to occur after massive transfusion of stored blood. This is believed to be due to a deficiency in the clotting mechanism, the exact nature of which has not been determined. Administration of multiple, large doses of calcium gluconate or vitamin K-1 oxide was of no apparent benefit. Previous experience has established the beneficial effects of fresh blood in patients who have a bleeding tendency after the administration of large amounts of stored blood. In this patient, it is believed that the use of fresh blood was lifesaving. However, a large quantity of blood (7 pints) was required before there was evidence that clotting occurred.

In the postoperative period, nasal oxygen was administered. About three hours after operation, respiration increased to 60 per minute. An intragastric tube was in place, but not functioning, and acute gastric distention occurred. This is not an uncommon occurrence in severely wounded patients. A larger tube was inserted, the distention was relieved, and the respiratory rate decreased to 40 per minute.

Postoperatively, the patient recovered rapidly. The pack was partially removed on the second day and the remainder on the fourth day without further bleeding.

This case emphasizes the value of replacement of blood loss with whole blood after injury.

SUMMARY

The use of massive quantities of blood may be required in the management of very severely wounded patients. A case is reported in which a patient received 23,350 c.c. of blood in the first twenty-four hours after injury. Several interesting factors in the initial care of patients who have sustained severe injury, accompanied by unusually great blood loss, are discussed.

ADDENDUM

After we had returned to the United States, an additional follow-up query was sent to Osaka Army Hospital and it was learned that the patient had developed a subcutaneous evisceration. At operation the bowel was inadvertently entered and a jejunal fistula developed. He expired on the seventy-sixth postinjury day.

Post-mortem examination revealed jejunal fistula, peritonitis, bronchopneumonia, and cerebrospinal leptomeningitis.

GLOMUS TUMOR OF THE STOMACH

Case Report

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IT HAS been well established that glomus tumors may exist in various parts of the body. A survey of 240 cases in eighty-nine reports demonstrates this lesion in regions other than the cutaneosubcutaneous junction. These

Fig. 1.—Photograph demonstrating gross polypoid lesion of greater curvature (greater omentum attached).

have been described in the deeper tissues such as joint capsules and striated muscle. It is felt that they are enlarged encapsulated glomera, easily removable, and do not recur. In only one reported instance has a glomus tumor displayed progressive, infiltrative growth.

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No lesion had been found involving the viscera until Stout and Kay reported three cases of glomus tumor of the stomach. This report represents the fourth case of a glomus tumor occurring in the stomach.

CASE REPORT

N. R. H. #212942. A 53-year-old white man was admitted to the New Rochelle Hospital on Feb. 12, 1953, shortly after having experienced a sudden bout of hematemesis sufficient to cause him to faint at home. The onset was marked by a sensation of weakness, followed closely by vomiting of about one pint of liquid and bright and clotted blood, and then by prostration. He was hospitalized immediately by his physician (Dr. W. P. R.).

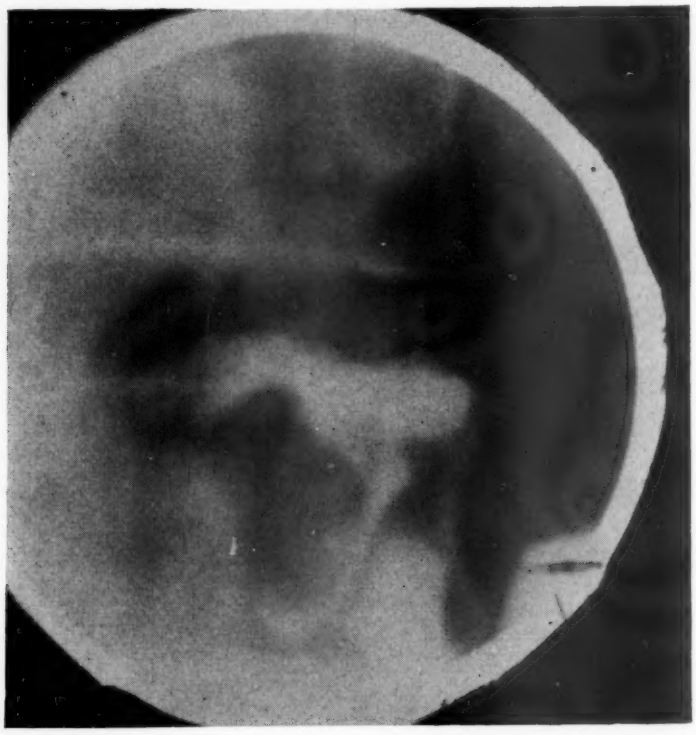

Fig. 2.—Spot film showing lesion on greater curvature.

Past history dated back about ten years, with recurring abdominal pain ascribed to diverticulosis and diverticulitis of the sigmoid colon. There had never been any accompanying melena. During the two months preceding the present admission he noted belching, heartburn, and loss of appetite. He was placed on Banthine, sedatives, and a bland diet, which he followed poorly.

When seen on admission, he was conscious with a blood pressure of 90/60 and a pulse rate of 96. He had a distinct pallor, although the hemoglobin was 86 per cent. There was no abdominal pain or tenderness on admission.

The admitting impression was that of hematemesis, etiology undetermined, most probably bleeding duodenal ulcer.

Treatment was conservative. Despite numerous transfusions the hemoglobin fell to 63 per cent by the fifth day. There was no further hematemesis but there were several tarry stools. Under appropriate treatment, from the sixth day on there was improvement in his clinical and laboratory picture. On the fourteenth hospital day an

upper gastrointestinal survey demonstrated outpouching of the greater curvature of the stomach in the prepyloric region. This was interpreted as a prepyloric greater curvature ulcer.

Surgical exploration of the lesion was carried out on the twentieth hospital day through a transverse incision in the upper abdomen.

Fig. 3.—Glomus tumor (×100, reduced ⅕).

The gross findings at surgery were as follows: There was a firm nodule visible on the serosal surface of the stomach 2 cm. in diameter. It was situated on the greater curvature of the stomach in the prepyloric region. There was a cluster of dilated blood vessels in and surrounding the lesion. The vessels appeared to penetrate all the layers of the gastric wall, and the mass was ulcerated on the mucosal surface. Frozen-section examination of the tumor was reported as benign, probably a carcinoid. A Billroth I resection of the stomach was performed. The postoperative course was not remarkable except for delayed emptying of the stomach which persisted for about two weeks. At

the time of discharge on the twentieth day after surgery there were no digestive disturbances. At the time of this writing, eighteen months after operation, the patient is entirely free of symptoms.

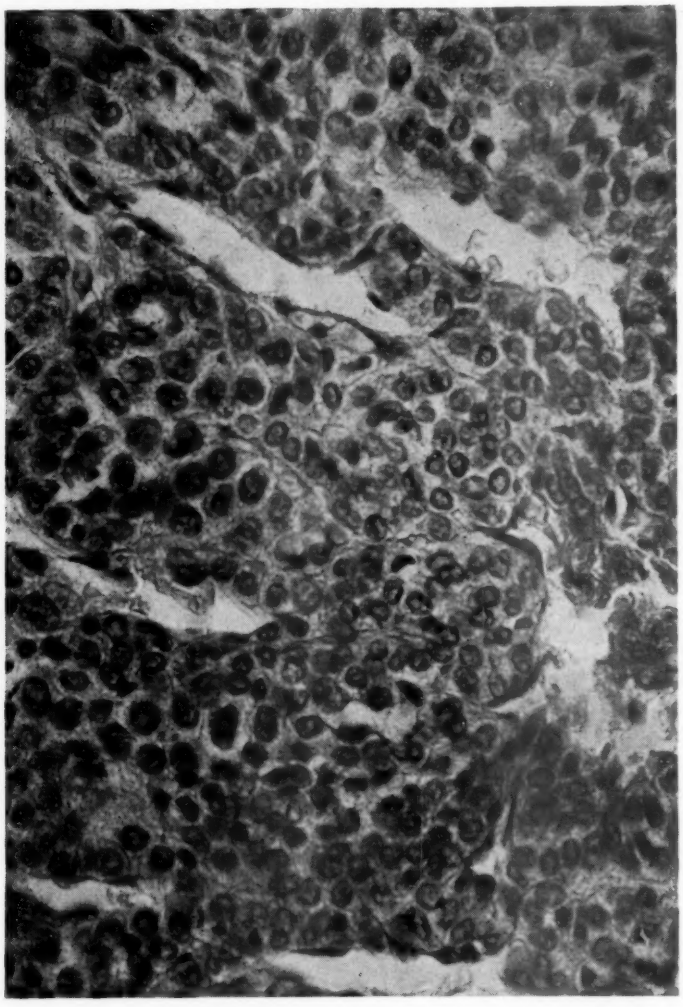

Fig. 4.—Glomus tumor (×100, reduced ¼).

Pathologic Examination.—

Gross: Presenting on the greater curvature and the posterior wall of the resected stomach about 1 cm. from the pyloric ring was a papillary cobblestone lesion projecting above the serosal surface. It measured 34 mm. in greatest diameter and was raised as high as 12 mm. above the serosa. The surface was covered by numerous nodules varying from 2 mm. up to 1 cm. in diameter. The posterior surface was similarly involved. On resecting the gastrocolic omentum it was demonstrated that the lesion consisted of a nodule the size of a walnut lying on the greater curvature and extending into the anterior and posterior walls of the stomach on the mucosal side. The lesion was adherent to mucosa. There were two distinct points of mucosal ulceration up to 5 mm. in diameter. Cross section through the walnut-sized tumor revealed the presence of numerous lobules of firm tan tissue separated by depressed homogenous gray fibers. The tumor appeared to be poorly encapsulated and blended intimately with the adjacent gastric musculature. No palpable lymph nodes could be demonstrated.

Histology: Multiple sections revealed numerous vascular spaces lined by flattened endothelial cells. Surrounding these vascular spaces were sheets of cells having poorly defined borders. The cells were polyhedral in shape. The nuclei were ovoid and showed no variation in size, shape, or staining reaction. There was a sparsity of mitotic figures. The lesion was fairly homogenous in most areas. At the periphery of the lesion, nests of vascular spaces cuffed by polyhedral cells were seen within the gastric musculature. In other spaces there was noted hyaline degeneration of the neoplasm. Scattered throughout the hyaline connective tissue were remaining clusters of polyhedral cells. In areas, the neoplasm had encroached upon the mucosa with resultant erosion.

The slides were reviewed by Arthur Purdy Stout, M.D., who agreed with the diagnosis of glomus tumor of the stomach.

DISCUSSION

There are certain points of similarity in this case with those reported by Stout and Kay. All cases now reported have been in men in the middle decades of life, this patient being 53, the others 46, 50, and 43. In this instance and in two others, massive gastrointestinal bleeding was the presenting feature. The distal end of the stomach has been the site of tumor in all four cases. Carcinoid tumor was initially suspected in all four cases.

SUMMARY

A case of glomus tumor of the stomach is presented.

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Editorial

Management of Pancreatic Pseudocysts

ONLY a small percentage of pancreatic pseudocysts can safely be managed by total excision. Some type of drainage must be established in the majority of cases. The disadvantages of marsupialization and external drainage are obvious. The procedure is associated with some mortality and with a much higher morbidity. Persistent fistulous drainage, excoriation of the abdominal wall, premature closure of the sinus tract with reformation of the cyst, alternating periods of drainage and of cessation of drainage associated with pain and apparent redistension of the cyst are far too commonly observed.

Since Jedlicka in 1921 first suggested internal drainage by cyst-gastrostomy, the merits and disadvantages of internal drainage have been much debated. Some have advocated one, some another, hollow viscus as preferable for anastomosis to the cyst wall—stomach, gall bladder, duodenum, jejunum. From the standpoint of ease of execution and dependency of drainage the jejunum would seem ideal. Of the first eleven reported patients treated by simple side-to-side anastomosis of cyst and jejunum, death from infection occurred in two, and in one, barium studies clearly revealed reflux of jejunal contents into the cyst cavity. In order to obviate the hazard of contamination of the cyst by intestinal contents and infection, jejunojejunostomy between afferent and efferent loops was suggested, and a short while later Roux-Y cyst-jejunostomy. There are available in the literature nine single case reports and one report of two cases so managed in addition to those of my associates and myself. We have now treated six consecutive cases of large pancreatic pseudocysts by side-to-end anastomosis of the cyst wall to a Roux-Y jejunal limb. All seventeen cases have been successful. There has been no mortality and no morbidity. There has been no recurrence and nothing to suggest infection of the cyst. This procedure has been amply demonstrated to be safe and effective. It has the advantage of ease of performance, dependency of drainage, and apparent freedom from the threat of infection of the cyst cavity through regurgitation of intestinal contents. It can be highly recommended in cases in which excision is not technically feasible or seems hazardous.

—Harris B. Shumacker, Jr.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

THE PROBLEM OF PROGNOSIS IN CANCER OF THE BREAST

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INTRODUCTION

PROGNOSIS in breast cancer is influenced by many factors in addition to the type of therapy. The effects of these influences are subtle and difficult to measure. Contemporary opinions concerning the local origin and subsequent spread of breast cancer indicate that an interval of time does exist in this disease between the period of onset and the ravages of spread. However, the length of this interval prior to metastases varies, and the precise period in each patient is unknown. One can never predict with certainty that therapy will be either curative or hopeless. If we are to evaluate the best treatment methods and to assess the survival results with accuracy, it is necessary to consider the natural history of breast cancer and the factors which influence its prognosis.

DURATION OF LIFE IN UNTREATED BREAST CANCER

The ultimate result sought in the therapy of breast cancer, as aptly expressed by Shimkin,[66] is the permanent eradication of the mammary malignancy and the recovery of the patient. If a "cure" is not possible, then the goal to be achieved is retardation of tumor growth, with the prolongation of a useful and comfortable life. If prolongation of life is not possible, then the therapeutic aim should be directed toward the palliation of all distressing signs and symptoms, particularly the relief of pain.

The distinction between curative and noncurative types of therapy is usually quite sharply defined in the case of breast cancer. The clinical indication for radical mastectomy or any other type of curative therapy rests upon the valid statistical demonstration that a significant proportion of patients are alive and well at the end of a fixed period of time, as compared with the inexorable death toll occurring among untreated patients, death being due, of course, to the natural history of the disease. The distinction between therapeutic procedures designed merely to retard the progress of breast cancer and the purely palliative measures is usually less well defined.

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Shimkin pointed out that "statistical analysis of final results on sufficient numbers of adequately controlled cases is the only method by which prolongation of life, or cure, can be acceptably substantiated." This, quite naturally, involves a comparison of a large series of treated patients with a similar series of untreated controls.

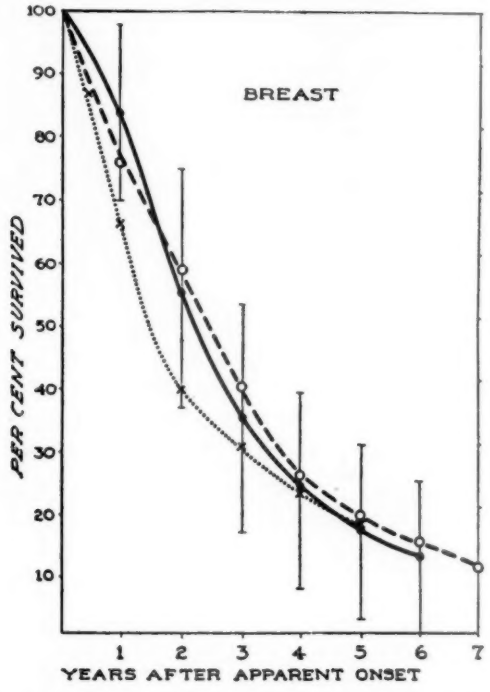

Fig. 1.—Duration of life from the onset of disease to death in untreated cancer of the breast. The vertical lines are probable errors of the means of Greenwood's data.
Key:
———— (Greenwood)
- - - - - (Nathanson and Welch)
. . . . . (Forber)
(From Shimkin, *Cancer*, January, 1951.)

Information regarding the natural history of untreated breast cancer has been collected and reported in the medical literature from many countries. Despite the obvious limitations and intrinsic errors of determining the exact date of onset in cases of breast cancer, the collected data for duration of disease have a definite place of medical importance. The most comprehensive and reliable early studies on the subject of the natural duration of cancer were published by Major Greenwood[21] using British data collected by Lazarus-Barlow and Leeming,[42] Wyard,[82] and others, from 1882 to 1924. Similar statistics were reported in London by Forber[17] and in the United States for a later period by Nathanson and Welch.[54]

The duration of life in untreated cancer of seven sites (from apparent date of onset to date of death) is summarized in Table I.

These data for breast cancer, portrayed in graphic form and combined with similar statistics from Forber and Nathanson and Welch, are shown in Fig. 1. There appears to be a rather close agreement between these three

sets of data derived from different geographical regions and covering varying time periods from 1882 to 1935. The validity of the results by virtue of their similarity alone is thereby enhanced.

TABLE I. NATURAL HISTORY OF UNTREATED CANCER

SITE	NO. OF CASES	MEAN AGE AT ONSET (YR.)	MEAN DURATION OF DISEASE (MO.)
Breast	651	57	38
Rectum	887	55	27
Cervix	1,749	48	21
Oral cavity	369	57	17
Stomach	154	52	17
Larynx	129	52	15
Esophagus	299	55	12

After Greenwood,[21] 1926.

One of the most important points to be carefully considered in the natural history of breast cancer is the number of untreated or inadequately treated patients who may survive for unusually long periods of time. On occasion a woman with a verified breast cancer will resort to a unique therapeutic regimen and by implication alone will attribute her long-term survival to the protective charm of some occult remedy. Explicit knowledge of the natural history of breast cancer with its occasional instances of spontaneous regression or long-term periods of quiescence and survival emphasizes the extreme caution that must be exercised in this disease in the evaluation of the effect of any form of therapy in each individual patient.

DURATION OF LIFE IN TREATED BREAST CANCER

Advancement of the Disease.—Despite a vast medical literature, it is readily apparent that the postoperative survival of patients with breast cancer is dependent upon many varied factors. The difficulty of precisely evaluating these factors is inherent in the science of statistics, which has become, as noted by the *British Medical Journal*,[13] "vastly elaborate, and the exclusion of disturbing variables is an advanced mathematical exercise. Consequently, a statistical analysis presents a structure so intricate, so specialized, and so formidable that this complicated erection has to be taken to pieces by an expert before a flaw can be detected in some small piece of the mechanism, upon which the whole working depends." To surgeons, therefore, statistics are neither sacred nor profane but merely regarded with some reserve, especially as they pertain to arguments alleging one method of treatment to be superior to another. While exact statistical data must be used to measure comparative differences in treatment and survival, yet the reaches of statistical science have their limits. Perhaps the basic human material which is the key to biostatistics is not sufficiently tempered with known facts to fulfill the difficult task which it is called upon to perform.

Modern statistical research has, however, rendered surgery a service by ruffling the feathers of current complacency regarding the expectations from

several types of surgical therapy. The selective limitations of radical mastectomy must be appreciated, and alternative modes of treatment in certain cases then will come to be regarded in a more favorable light. This will create an eclectic attitude toward the problem of breast cancer and its treatment.

Although our ultimate hopes may rest with the endocrinologist, the virologist, or the experimental chemotherapist, yet in the surgical treatment of breast cancer our current strategy is based upon the belief that there is a stage when, apart from a few stray cells which may lie dormant within the embrace of the body defenses, the growth of malignant cells is confined to the breast and accessible regional nodes. The classic Halsted radical mastectomy provides a rampart of preservation for these patients. Whereas differences in survival between modes of surgical therapy might be very small and might require the most careful statistical analysis to reveal them, yet these very small differences are of supreme importance to the individual patient who survives.

A long-term follow-up survey of all patients with primary breast cancer who received surgical treatment at The Johns Hopkins Hospital during the period 1935 to 1940 inclusive was reported by Lewison, Trimble, and Griffith.[49] A total of 255 patients, both private and ward, Negro and white, entered the hospital with a clinical diagnosis of breast cancer. Two hundred twenty of these patients subsequently underwent operation; fourteen were treated by simple mastectomy, 204 by radical mastectomy, and two by local excision (one patient having pulmonary metastases and the other refusing further treatment). The remaining thirty-five patients either were treated by radiotherapy alone, were considered to have lesions hopelessly advanced and beyond treatment, were discharged without treatment, or refused treatment.

A successful follow-up was obtained in 208 patients, or 94.5 per cent of the series. All patients lost to follow-up or those dying of intercurrent disease were considered dead of breast cancer for the purpose of this computation.

The presence or absence of axillary node involvement is of paramount importance and of decisive influence in predicting the prognosis of patients with breast cancer. Table II records the five-year survival rate at The Johns Hopkins Hospital for (1) those patients without axillary metastases by microscopic examination (64.1 per cent five-year survival) and (2) those patients with axillary metastases by microscopic examination (31.7 per cent five-year survival).

The total five-year survival rate for all patients regardless of the type of surgical treatment or the stage of the disease was 43.2 per cent. The so-called clinical "cure" rate—patients living and well without discernible evidence of recurrence of metastases at the end of five years—was 38.2 per cent. Axillary metastases were noted in 62 per cent of patients who were subjected to radical mastectomy. When surgical treatment consisted of radical mastectomy, almost two-thirds of the patients without axillary metastases were still alive five years after operation, whereas only one-third of the patients with axillary metastases were alive at the end of this period.

TABLE II. FIVE-YEAR END RESULTS OF SURGICAL TREATMENT FOR BREAST CANCER (1935-1940)

TYPE OF TREATMENT	STAGE OF DISEASE	NO. OF PATIENTS	LIVING AND WELL		LIVING WITH RECURRENCE		TOTAL SURVIVORS	
			NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Radical mastectomy	Breast alone	78	44	56.4	6	7.7	50	64.1
	Breast and axilla	126	35	27.7	5	4.0	40	31.7
	Total	204	79	38.7	11	5.4	90	44.1
Simple mastectomy	Breast alone	5	2	40.0	—	—	2	40.0
	Breast and axilla	9	2	22.2	—	—	2	22.2
	Total	14	4	28.6	—	—	4	28.6
Local excision	Breast alone	1	1	100.0	—	—	1	100.0
	Breast and axilla	1	—	—	—	—	0	0.0
	Total	2	1	50.0	—	—	1	50.0
Total		220	84	38.2	11	5.0	95	43.2

The ten-year end results of surgical treatment are shown in Table III. The over-all ten-year survival rate for this hospital was 29.1 per cent. If cancer remained confined to the breast alone, however, the ten-year survival rate was 47.6 per cent. On the other hand, if breast cancer had already spread to the adjacent axilla, the ten-year survival rate fell to 17.6 per cent. The importance of metastases to the regional nodes in the prognosis of breast cancer is obviously of salient significance.

TABLE III. TEN-YEAR END RESULTS OF SURGICAL TREATMENT FOR BREAST CANCER (1935-1940)

STAGE OF DISEASE	NO. OF PATIENTS	LIVING AND WELL		LIVING WITH RECURRENCE		TOTAL SURVIVORS	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Breast alone	84	34	40.5	6	7.1	40	47.6
Breast and axilla	136	23	16.9	1	0.7	24	17.6
Total	220	57	25.9	7	3.2	64	29.1

Harrington[31] has presented the fifteen-year to forty-year survival rates for breast cancer following radical mastectomy performed at the Mayo Clinic. Whereas no method of predicting the prognosis is valid in any individual case, the factors of importance in the prognosis of breast cancer, as indicated by Harrington, are as follows:

1. The extent of the malignant involvement at the time of operation.
2. The degree of malignancy as shown by microscopic examination of the primary tumor.
3. The presence of such associated conditions as pregnancy and lactation.
4. The presence of constitutional diseases such as diabetes.

The most important of these factors is the extent of the disease at the time of operation as indicated by the presence or absence of axillary nodal metastasis found microscopically at the time of operation. The prognosis is

decidedly more favorable in patients in whom the axillary lymph nodes are not involved by metastatic spread than in those patients in whom axillary spread is found to be present at operation.

An important factor in prognosis is the natural resistance of the tissues of the host to the growth and spread of cancer. There is no known method of evaluating this property of normal tissues to resist malignant disease. However, host resistance must vary from time to time and from one person to another. It may inhibit the invasiveness and extension of the primary tumor locally, as well as act as a restraint to the more distant metastatic dissemination of breast cancer.

There were 4,637 patients who underwent radical mastectomy at the Mayo Clinic from 1910 through 1934, and of these there were 4,563 patients (98.4 per cent) who were successfully traced. The fifteen- to forty-year survival rates of these traced patients are summarized in Table IV.

TABLE IV. THE FIFTEEN- TO FORTY-YEAR SURVIVAL RATE FOLLOWING RADICAL MASTECTOMY FOR UNILATERAL BREAST CANCER IN WOMEN

YEARS P.O.	PATIENTS		LIVED INDICATED PERIOD	
	TOTAL	TRACED	NO.	%*
15 or more	4,637	4,563 (98.4%)	1,144	25.1
20 or more	3,615	3,544 (98.0%)	624	17.6
25 or more	2,439	2,391 (98.0%)	301	12.6
30 or more	1,415	1,375 (97.2%)	128	9.3
35 to 40	520	507 (97.5%)	35	6.6

After Harrington.[31] 1953.
*Based on traced patients. Inquiry as of Jan. 1, 1950.

It is indeed gratifying to note that 25.1 per cent of all patients operated upon by means of radical mastectomy almost a generation ago survived fifteen years or more.

There is considerable difference in the survival rates in each postoperative period between patients with and without axillary metastases. This noteworthy improvement over the years in prognosis has been found to be universally true.

The stage of advancement of breast cancer at the time of the first treatment is by far the most important single factor in assessing prognosis. The variation in the five-year survival rate from 80 to 90 per cent in those patients with early Stage I cancer to 5 per cent or less in patients with widespread metastases (Stage IV) exceeds that of any other known factor influencing prognosis. The results of treatment of breast cancer when the disease is considered by clinical stages have been reported by many clinical investigators. The prognosis in relation to stage of advancement of the disease at the time of treatment has been reported for the Royal Cancer Hospital by Smithers and associates[71] as in Table V.

Extent of axillary metastases: Although the most important factor in predicting the postoperative survival of patients with breast cancer has proved to be the presence or absence of metastases to the axillary or other accessory regional lymph nodes, there has been relatively little interest shown in the degree of this

axillary lymph node involvement. Warren and Tompkins,[78] in a small series, have carefully exploited the prognostic value of extent in the pathologic examination of axillary lymph nodes in breast cancer. The discrepancy between the clinical and pathologic findings of axillary involvement may introduce an error of considerable magnitude, and therefore the clinical estimate of extent of axillary metastases must be cautiously viewed with some doubt and uncertainty.

TABLE V

STAGE	NO. OF PATIENTS	5-YEAR ACTUARIAL SURVIVAL RATE (PER CENT)	STANDARD ERROR (PER CENT)
I	165	74.1	3.49
II	242	53.4	3.30
III	224	23.6	2.99
IV	138	8.8	2.46
Unstaged	54	52.0	6.98

Coller, Kay, and MacIntyre[6] and Davis and Neis[8] have shown that by special clearing techniques a substantially greater number of lymph nodes can be discovered than by the usual methods of examination, and that metastases occasionally occur in the small easily overlooked nodes. Saphir and Amromin[63] found a substantially higher incidence of obscure axillary lymph node metastases by a technique of serial sections. Metastatic cancer was found in 33.3 per cent of instances in which previous examination had not disclosed tumor in the nodes. While clearing techniques, serial sectioning, and the classifying of axillary nodes into apical, middle, and basal groups might give more accurate data, these methods are time consuming, expensive, and generally unsuited for routine use. However, a careful search of the gross specimen indicating total number of nodes found and number containing metastases is an important part of the surgical-pathologic routine.

The extent of involvement of axillary lymph nodes reveals that survival is inversely proportional to the number of axillary nodes containing metastases.

TABLE VI. EFFECT OF EXTENT OF AXILLARY METASTASES ON SURVIVAL

	NO. CASES	LIVING AND WELL AT 5 YEARS (PER CENT)
No metastases to axillary lymph nodes	81	85
Metastases involving less than 50 per cent of axillary nodes	22	68
Metastases involving more than 50 per cent of axillary nodes	31	38
Metastases involving 100 per cent of axillary nodes	37	19

After Warren and Tompkins.[78]

Curability, as well as survival time of patients ultimately dying of the disease, decreases as the extent of metastases to the axillary lymph nodes increases. Local recurrence is also likely to increase with greater axillary involvement. This increased incidence of local recurrence, as noted by Warren

and Tompkins, suggests that skin recurrences in the operative area may not be entirely a matter of local implants. Subcutaneous metastases or lymphatic extension of the primary disease may also account for these apparent regional recurrences.

The poor prognosis generally given in a case where only a few axillary nodes are involved is probably unwarranted. Those patients with metastases to only one or two nodes out of many uninvolved axillary nodes may have almost as good a chance for prolonged survival as those patients with no axillary metastases. Moreover, patients with most or all of their axillary nodes involved by cancer not only have a much poorer prognosis for life itself but also their period of postoperative survival is considerably shortened. A corollary to these conclusions, of course, concerns operative technique. The greater the number of axillary lymph nodes removed by a carefully performed radical mastectomy, the greater the chances of survival and the more accurate the prognosis.

Histologic Grading and Prognosis.—Opinions of clinicians and pathologists vary widely regarding the prognostic value of histologic grading in cancer of the breast. Von Hansemann[76] in 1893 is said to have been the first to introduce the concept of anaplasia and to attempt to correlate the histologic appearance of cancer with its clinical behavior. However, only scanty attention was paid to tumor grading until Broders[4] revealed a significant relationship between anaplasia and survival. Greenough[20] shortly thereafter studied the grade of malignancy of breast cancer and reported a parallel between the histologic picture and prognosis. Cellular differentiation and other cytologic criteria were considered by MacCarty[51] to be most important factors in the prognosis of breast cancer.

However, differences of opinion regarding the accuracy of histologic grading as an index of survival have varied from those who found as many as twenty characteristics of prognostic value to those who were unable to find even one. Reimann[60] concluded that it was futile to decide from an examination of the microscopic section what will happen to the patient. Plaut,[59] in a careful review of the literature, concluded that he could not advocate the method of histologic grading as an index of prognosis. Willis[81] believes that the precise numerical grading of malignancy is arbitrary and of little practical value. Broad grouping based upon general histologic structure may be helpful.

Warren and Tompkins do not ordinarily grade breast cancers because the personal equation in the process is too great. This is particularly true of the intermediate grades. There is, of course, a real need for some reliable method of assessing the degree of malignancy from a study of breast cancer histology. If histologic grading of biopsy specimens could only provide a more precise prognostic picture, it would certainly be of greater value than the vague statements of duration of disease or inaccurate clinical measurements of tumor size or site upon which we are forced to rely.

Tumor grading, however, is not without its serious difficulties. One small biopsy specimen may not be representative of the entire tumor, and metas-

tases are not necessarily the image of their primary progenitor. As noted by Richards,[61] tumor grading thus far has proved to be only partially satisfactory. An excellent survey of this problem has been presented by Bloom,[2] who advocated that prognosis be based upon tumor grading taken together with tumor staging (axillary lymph node metastases) as the most accurate indication of survival presently available. Clinical staging plus histologic grading was found to be of greater prognostic value than either method alone. This combined clinicopathologic system for determining breast cancer prognosis requires careful study and further confirmation.

However, as noted by Smithers and co-workers,[71] it is the clinician who has to gauge prognosis and decide upon treatment based on clinical staging of the disease without the benefit of pathologic examination. Whereas tumor grading is a reflection of wisdom of action already taken, clinical staging determines the wisdom of action about to be taken.

To determine if there might be any notable histologic characteristics peculiar to breast cancer patients with long-term survivals, Lewison, Trimble, and Griffith reviewed the histologic sections of sixty-four patients who were known to have survived ten years or longer. This differed from the usual practice followed in histologic evaluation of prognosis where microscopic sections are reviewed without the clinical course being foreknown.

In the examination of the sections the following factors were specially noted: (1) lymph node involvement, (2) vessel invasion, (3) pattern, (4) tubule formation, (5) cellular and nuclear morphology, (6) hyperchromatism, (7) mitoses, (8) necrosis, and (9) desmoplasia. For the most part, Stewart's[73] histologic classification of breast cancer was used.

In general it may be stated that no histologic characteristics that could be correlated with the prolonged clinical course were found in a review of these sixty-four carcinomas of the breast from women known to have survived ten years or longer. There were, however, several results of the study that warrant mention. It was notable that in only one case was the diagnosis of in situ carcinoma made, the other sixty-three cases showing definite stromal infiltration. In twenty-four cases (37.5 per cent) metastases were revealed in one or more lymph nodes. Not infrequently other findings also generally regarded as purporting a poor prognosis were noted, such as skin invasion and metastases to muscle. Tubule formation indicating a favorable prognosis was absent in forty-one (64 per cent) cases. It is interesting that adenocarcinoma, "comedo" carcinoma, and medullary carcinoma with lymphocytic infiltration, the histologic types of duct carcinoma usually associated with a better prognosis, were not especially conspicuous in this series. It is remarkable that the proportion of the histologic types of breast carcinoma noted in this long survival series is about the same as the proportion seen for all cases of breast carcinoma. These observations demonstrate that, at least in this series, the histologic appearances alone would not have allowed one to prognosticate the favorable ten-year survival that ensued.

Thus, the outlook for a patient with cancer of the breast depends first and foremost upon the extent of the disease when first discovered. Histologic

appearance and tumor grading are less important omens of prognosis but may be of ancillary benefit in determining the degree of radiosensitivity, other factors being considered.

Age.—Considering the cardinal factors which could conceivably modify the survival rate of breast cancer, age has been regarded by various investigators as an equivocal index of prognostic significance. Many authors contend that age has an important bearing on prognosis. The prevailing impression was voiced by Ewing,[15] who stated that "before thirty years of age mammary cancer is extremely fatal." It is a common but debatable doctrine that the younger the cancer patient, the less hopeful the outlook. On the other hand, Richards, in a critical clinical analysis of survival in 906 cases of breast cancer, concluded that there was no justification for the assumption that the prognosis was less favorable in young women merely because of age alone.

Yet breast cancer occurring before the age of 30 years is frequently considered to be a most ominous disease. Haagensen and Stout[24] indicated that some surgeons consider the condition categorically inoperable and refuse to perform definitive surgery. A special study of breast cancer in young women was undertaken by Lee.[43] He investigated 191 cases of patients treated by radical mastectomy, all of whom were under the age of 40. The three-year survival rate was only 40 per cent. Lee concluded that "cancer of the breast in young women is a much more menacing disease than it is in mid-life or old age." In commenting on these poor results Bloom[3] called attention to the lack of controls among older patients from the same clinic, as well as the inclusion of women with more serious lactation cancer in this selected series. The ill effect of pregnancy and lactation on breast cancer is a special problem which will not be discussed in this paper. The prognosis for these younger patients in whom pregnancy is a complication is particularly poor.

The over-all five-year survival rate for breast cancer patients at The Johns Hopkins Hospital was found by Lewison, Trimble, and Griffith to be 43.2 per cent. However, the five-year survival rate computed for patients under the age of 40 was only 29.6 per cent. Thus, a comparatively unfavorable prognosis for young women was demonstrated in this small series. Yet, it should be carefully noted that the breast and axilla were involved in 61.8 per cent of the entire series, whereas in the limited group of women under the age of 40, the breast and axilla were involved more often, in 70.4 per cent, thus indicating a more advanced stage of the disease at the time of operation.

In the case of breast cancer, destiny appears to grant no special favor to the young or to the mothers of the young. On the contrary, the view held by Nathanson and Welch, Cade,[5] Pack and Livingstone,[58] and others indicates that the prospects for this group are indeed unpromising.

However, there are those who find that age in itself is of little or no prognostic significance. In a collected series of seventy-three breast cancer patients all under the age of 30, de Cholnoky[11] found the five- and ten-year survival rate to be comparable to that of older age groups. Hawkins,[33] in an investigation of several thousand cases of breast cancer, concluded that the data did not support the contention that younger cancer patients have any

more somber outlook than older patients. The five-year survival rates in three age groups, (1) patients under 49, (2) patients 50 to 59, and (3) patients over 60, were generally comparable.

Lane-Claypon[40] demonstrated a similar five-year survival rate among 530 collected cases of breast cancer when considered by decennial age periods. "The figures do not bear out the suggestion that there is any inherently greater malignancy in cancer among young persons, unless the growth is allowed to extend beyond the breast, when the results are more unfavorable." In a later study Lane-Claypon[41] analyzed a larger series of cases and divided them into three age groups, (1) patients under 40, (2) patients 40 to 59, and (3) patients aged 60 or over. From a study of her end results Lane-Claypon concluded that the prospects for "cure" were certainly no less favorable in young patients with breast cancer than for those nearer the end of their normal physiologic life span.

In a large series of cases studied at the Mayo Clinic, Harrington[29] found that age alone had no significant bearing on the prognosis. The proportion of patients with and without axillary metastases in the majority of age groups appeared comparable.

Bloom noted a considerable fluctuation in the prognosis of patients in the several age groups which he studied. "No parallel is revealed between age and outcome, and there is no support for the view that the tumours of younger women, apart from those associated with pregnancy and lactation, kill more rapidly."

In an interesting survival study by Richards, the cases of breast cancer were grouped in relation to the menopause (Table VII): (1) prior to menopause, (2) concurrent with the menopause or up to five years after, and (3) five years after the menopause or longer. From a careful examination of the five- and ten-year survival rates, there appeared to be very little significant difference in the total five-year survivals in the three groups. If anything, the premenopausal group seemed to have the best prognosis. Compounding the caprice of these biostatistics, Richards found that the menopausal group seemed to have the poorest ten-year survival rate.

Wade,[77] in a comparative study of results, found that the survival of 649 women with untreated breast cancer was uninfluenced by age alone. At the Royal Cancer Hospital, Smithers and his colleagues found that there was some tendency for prognosis to vary with age, "being comparatively good in younger women, being poor in women in their fifties, improving again in the sixties and seventies, and being bad in the aged." In 846 patients treated at the Royal Cancer Hospital the five-year survival rate recorded in relation to age when first seen at the hospital was as shown in Table VIII.

Haagensen and Stout[25] have periodically reviewed their end results and have found a comparatively good prognosis for younger patients. Youth is not considered a contraindication to radical mastectomy. Since most observers agree that the rate of growth is perhaps slower in the older patient with breast cancer, Haagensen regards these patients as most amenable to surgical therapy. ". . . We do not hesitate today to perform radical mastectomies on women

of advanced age, including those in their eighties, even when they have a considerable degree of cardiovascular disease."

It is the opinion of Geschickter[18] that certain unfavorable biologic features exist for younger women with breast cancer but, as emphasized by Kaae,[35] these differences may be compensated for by the fact that younger patients tend to seek medical attention much sooner than older patients. This has been also noted at the Radiumhemmet in Stockholm by Nohrman.[56] Similarly, Lewison and associates[48] have found that young women are more alert and receptive to the danger signals of breast cancer and to cancer education generally as evidenced by their response to the teaching of breast self-examination.

TABLE VII. MAMMARY CARCINOMA: SURVIVAL IN RELATION TO MENOPAUSE

	STAGE	NO. OF CASES	5-YEAR SURVIVAL	NO. OF CASES	10-YEAR SURVIVAL
Premenopausal group	I	68	83%	31	65%
	II	65	60%	36	42%
	III	158	46%	62	26%
	IV	34	15%	13	8%
	V	15	7%	5	0%
	Total	340	51%	147	35%
Menopausal group	I	31	90%	7	43%
	II	35	40%	18	11%
	III	66	29%	26	8%
	IV	25	16%	9	11%
	V	4	0%	3	0%
	Total	161	40%	63	13%
Postmenopausal group	I	50	78%	18	55%
	II	86	58%	38	32%
	III	173	35%	61	18%
	IV	80	16%	26	7%
	V	20	0%	4	0%
	Total	409	40%	147	24%

GENERAL SUMMARY FOR COMPARISON
ALL CASES (1,189)—1933-1943

	I	II	III	IV	V	TOTAL
5-year survival	81%	54%	28%	16%	3%	43%
10-year survival	59%	28%	21%	8%	0%	26%

After Richards,[61] 1948.

TABLE VIII

AGE (YR.)	NO. OF PATIENTS	5-YEAR ABSOLUTE* SURVIVAL RATE (PER CENT)
21-30	4	25.0 (28.3)
31-40	90	43.3 (44.0)
41-50	199	48.3 (49.7)
51-60	240	29.0 (30.9)
61-70	197	38.1 (44.7)
71-over	116	23.9 (38.5)
	846	36.5 (41.1)

*The figures in parentheses are the absolute survival rates corrected for expected number of deaths from other causes.

Geschickter found the average postoperative duration of life in patients younger than 40 to be 3.45 years, compared to 5.5 years for patients older than 40. Sistrunk and MacCarty[69] noted that 41.7 per cent of patients over 50 years of age were living five to eight years after operation, as compared with

only 31.8 per cent of patients under 50. Whereas the five-year survival rate may be more or less comparable regardless of age, the rapid termination of tumors which prove to be fatal in the young person seriously shortens the average postoperative period.

Those authors who claim that a relationship exists between age and prognosis usually maintain that the breast cancers of younger patients tend to be more anaplastic than do those of older patients. If this were true, Bloom suggested that one would expect to find a greater proportion of breast cancers of a highly malignant histologic grade among younger patients. However, in a study of age, grade of tumor, and prognosis, Bloom found a remarkably even distribution of high- and low-grade malignancies in the various decades of life. Correlating the cytology and histology with age and prognosis in accord with his criteria gave no support to the belief that cancer of the breast is any more malignant in younger patients. Whereas these results are in general agreement with those of Lees and Park,[46] they are in direct disagreement with the earlier studies of Taylor.[74] Using the principles of histologic grading recommended by Greenough, Taylor found a larger number of breast cancers of a high order of malignancy among young women.

Thus, the influence of age alone on the prognosis of patients with breast cancer appears to be exceedingly difficult to determine. In the realm of biostatistics, the simple truth, which is often at the mercy of so many nonmeasurable biologic variables, may be impossible to verify. Therefore, by reviewing the current literature it is quite possible for sound and reasonable surgeons to hold conflicting points of view regarding the prognostic significance of age in breast cancer. The prevailing impression (all extraneous factors being biologically equal) that the younger the patient the poorer the prognosis remains a prophetic imponderable.

Duration of Disease.—In many instances of breast cancer a distinction will be evident in the case history between those "lumps" which have appeared suddenly or have had a rapid onset and those which have grown slowly over a long period of time. As noted by Richards, tumor size and duration of disease are often expressions of the degree of malignancy, which may have an important bearing on ultimate prognosis. Although an accurate history is frequently difficult if not impossible to obtain regarding the true duration of disease, yet full use of all pertinent information concerning time should be made whenever possible. A brief history may be indicative of an intelligent and observant patient anxious to detect an early cancer or, on the other hand, it may merely reflect fear, ignorance, or an unobservant patient with an advanced lesion. Data regarding the duration of the disease are dependent upon the patient's memory and upon an innate tendency to tamper with the truth of time in accord with one's feelings and the tone of the physician's question.

Interpreted with a certain degree of reservation, the influence of the fundamental factor of "rate of growth" on survival was studied by Richards in 324 cases of breast cancer (Table IX). Accurate data in these patients were presumed to be available. The prognosis was found to be most favorable when the rate of growth (or mitotic interval) was slowest.

Fighting cancer by means of public education has resulted in shortening the period of delay between apparent onset and definitive treatment. Toward the end of the last century, Dietrich,[12] in 1892, reported that in only 23 per cent of the cases in his series was the duration of symptoms less than six months. Halsted[26] reported that nineteen of seventy-six operations for breast cancer were incomplete "because of the magnitude of the growth and the hopelessness of the case." He considered breast cancer "a curable disease if operated upon properly and in time. I cannot emphasize too strongly . . . not losing a day. . . ."

TABLE IX. RATE OF GROWTH VERSUS SURVIVAL: MAMMARY CARCINOMA 1939-1941

RATE OF GROWTH	TOTAL NO. OF CASES	ALIVE AFTER 5 YEARS
Slow: less than 1 cm. per 6 mo.	55	84 %
Moderate: 1 cm. per 6 mo.	104	63.5%
Fast: more than 1 cm. per 3 mo.	139	18 %
Rapid: (Inflammatory)	26	4 %
Total	324	43 %

After Richards.[61]

Reports from the United States and many foreign countries indicate that more patients are now being seen earlier in the course of their disease. According to Harrington[30] of the Mayo Clinic, during the period 1910 to 1914 only 32.6 per cent of the patients were operated upon within six months from apparent onset, compared with 56.4 per cent operated upon within six months during the period 1935 to 1939. Lewis and Rienhoff,[47] reporting the early Johns Hopkins Hospital breast cancer cases, found only 34 per cent of the patients seeking medical care within six months. In New York, Eggers, de Cholnoky, and Jessup[14] found that only 36.6 per cent of their patients reported for treatment within the first six months. In a careful review of London's Middlesex Hospital cases during the years 1936 to 1942, Bloom found that 65 per cent of the patients came for treatment within six months of their first symptom and 85 per cent came within twelve months.

The length of time from the observation of the first symptom to the time of definitive therapy was reported recently by Kaae for the Radium Center of Copenhagen. Table X shows that about one-third (32 per cent) of the patients came under treatment within one month, about one-half (52 per cent) within three months, and about two-thirds (67 per cent) within six months. There appeared to be no significant difference between the various age groups.

TABLE X. LENGTH OF DELAY BETWEEN OBSERVATION OF FIRST SYMPTOM AND INSTITUTION OF ADEQUATE TREATMENT IN CARCINOMA OF THE BREAST IN WOMEN

AGE AT OBSERVATION OF FIRST SYMPTOM (YR.)	2 WK. OR LESS (%)	1 MO. OR LESS (%)	3 MO. OR LESS (%)	6 MO. OR LESS (%)	12 MO. OR LESS (%)	TOTAL NO. OF CASES
<40	18	31	49	64	84	45
40-49	16	32	49	67	82	109
50-59	16	34	57	71	80	129
60-69	19	31	51	67	80	118
≥ 70	22	31	47	64	82	74
All ages	18	32	52	67	81	475

After Kaae,[35] 1948.

Nohrman found that the average duration of symptoms before reporting to a doctor in patients attending the Radiumhemmet was 8.8 months. Among 2,129 women with breast cancer in England, Hartnett[32] found that 56 per cent had symptoms for three months or more, and 41 per cent had symptoms for six months or more, before consulting a doctor.

The duration of disease on admission was found by Haagensen and Stout to vary strikingly between private and ward patients. Private patients reported much earlier for treatment than did ward patients. During the first month after onset, more than twice as many private patients (37.1 per cent) sought care than did ward patients (16.7 per cent). The reasons for this promptitude are not entirely clear, but curiously enough they appeared to have no direct bearing on the end results in this series.

The average duration of symptoms in several large series of cases was found to be as follows (after Kaae):

TABLE XI

AUTHOR	YEAR	DURATION OF DISEASE (MO.)
Dahl-Iversen	1927	9.5
Wevill	1932	14.7
Nathanson and Welch	1936	12.0
Andreassen	1947	3.0

Warren and Witham,[79] in an early study of metastatic patterns in 158 autopsied cases of breast cancer, noted that the average delay from apparent onset to operation in 113 cases was ten months, and the average survival from operation was thirty-six months, for a total duration of the disease of forty-six months. Lee and Tannenbaum,[45] in a study of 363 patients treated by irradiation alone, found the duration of the disease to be fifty-three months. The average period from recurrence to death was twenty-four months.

Perhaps it is well to consider the views which have been expressed regarding the duration of disease as an index of prognosis. Luff,[50] in a study of over 1,500 cases for the British Medical Association, found that the longer the period of delay, the poorer the prognosis. The four-year survival rate for patients receiving treatment during the first month was twice as high as for patients receiving treatment after twelve months.

Hoopes and McGraw[34] noted that the five-year survival rate decreased as the duration of the disease increased. This occurred in patients both with and without axillary metastases. MacDonald[52] found the most favorable survival rate in those patients who received surgical treatment within two months after discovering their tumors. Following this period a rapid deterioration in prognosis occurred. However, with a delay of one year or more the survival rate suddenly and rather surprisingly increased. Eggers, de Cholnoky, and Jessup reported a five-year survival rate of 76 per cent for patients operated upon within one month. The survival rate decreased rapidly with increasing duration of symptoms, falling to 20 per cent for a delay of one to two years. With further procrastination, however, the results improved, from 25 per cent for a lapse of two to three years to 41 per cent for an even longer interval.

Nathanson and Welch found that patients with the shortest delay in treatment actually had the worst prognosis, whereas Lewis and Rienhoff, Kunath,[39] Hawkins, and Wevill[80] failed to find any significant difference whatsoever.

Perhaps one explanation for the fact that the prognosis does not continue to deteriorate with the duration of the disease lies in the convincing concept that the more malignant and rapidly growing breast cancers receive earlier attention and treatment whereas, conversely, the slow-growing cancers receive later attention and treatment. Korteweg[36] as early as 1880, pointed out with remarkable clinical discernment that breast cancer patients with the longest period of symptoms frequently showed the most favorable end results. The survival of certain patients with late cancer with a low order of malignancy (or perhaps a high order of host resistance) was allowed to proceed during a prolonged period of delay by the laws of natural selection.

Kaae found that operability depended upon the time which elapsed from the first symptom until definitive therapy was instituted. All patients who reported for treatment within the first two weeks were technically operable (Table XII). In those cases in which patients came under treatment within two weeks, 59 per cent were in Stage I, 41 per cent were in Stage II, and there were none considered inoperable. With increasing duration of symptoms, the number of cases in Stage I became steadily less, and there was a gradual increase in the number of cases classified as inoperable. Kaae concluded that in the treatment of breast cancer, "it is of paramount importance for the result that adequate therapy is instituted as early as possible after the appearance of the first symptoms. This can only be achieved if the patients consult a physician as soon as they have noticed the first signs which might point to cancer of the breast, and if the diagnosis is established as soon as the case gets into the hands of the physician." What is gained in prognosis by the patient seeking medical care early must not be lost by the physician in procrastination or watchful waiting!

TABLE XII. RELATION BETWEEN DELAY AND OPERABILITY AND BETWEEN DELAY AND STAGE OF DISEASE

DELAY	NO. OF CASES	TECHNICALLY OPERABLE (%)	ALL CASES		
			STORAGE I (%)	STORAGE II (%)	INOPERABLE (%)
2 weeks or less	84	100	59	41	0
2 weeks—1 month	69	94	53	41	6
1-3 months	92	89	43	46	11
3-12 months	140	77	31	46	23
Over 12 months	90	71	41	30	29
	475	85	44	41	15

Modified after Kaae,[35] 1948.

The relationship between duration of disease on admission and the five-year clinical cure rate has been carefully recorded by Haagensen and Stout.[23, 25] In their 1915 to 1934 series of cases, the cure rate fell, as expected, with increasing duration of disease. However, the data in the 1935 to 1942 series curiously failed to show this correlation.

Bloom, in a critical study of duration of symptoms and prognosis, found the survival rate to be uniform regardless of the delay. However, a slight difference in survival rate was noted when the histologic grade of malignancy was considered in relation to duration of disease and prognosis. Time appeared to be of importance only for tumors of low-grade malignancy. The prognosis in "highly malignant" breast cancers (Grade III) appeared to be uninfluenced by the duration of the disease. The survival rate was equally bad for these patients regardless of when they reported for treatment. It was believed by Bloom that by the time such breast tumors were detected and diagnosed the disease had already advanced well beyond the breast itself. Kreyberg and Christiansen[38] have studied the same problem, considering the grades of breast tumors, and have supported the conclusions of Bloom. As noted by Kreyberg,[37] however, these conclusions may be true for groups of cases, but in each individual case, independent behavior based upon many factors makes prognosis much less predictable.

The statistical analysis of Shimkin and his colleagues[68] in 1,038 cases of breast cancer shows that there appears to be a significant difference in the several stages of disease which are closely related to the duration of delay. The median period of delay for Stage I and Stage II was 4 months and 5.5 months, respectively, whereas the median period of delay for Stage III was 11.5 months, and for Stage IV it was 25.0 months. These differences are striking and statistically highly significant.

In a critical computation of the mean survival of women with cancer of the breast, from apparent onset to five years after treatment, according to delay, Shimkin and co-workers have shown that the average patient lives for forty-five months if there has been less than one month of delay, whereas the average patient lives for sixty-six months if there has been a delay of thirty-six months. These data, of course, must not be distorted to suppose that delay is desirable. Such is certainly not the case. Presentation of survival data which takes into consideration duration of delay and stage of disease is at the mercy of biologic selection. Cases of rapidly growing and highly fatal malignancies fall into one end of the survival scale whereas slow-growing tumors fall into the other end of the scale. The tremendous influence of the biologic properties of tumor activity and host resistance is clearly demonstrated.

The results of most analyses indicate that delay has a definite influence in determining the clinical stage of the disease, its operability, and its prognosis. It is occasionally true, despite the apparent paradox, that even a long delay in some cases may not adversely alter the stage of the disease or the prospects for survival. Conversely, the least delay possible does not necessarily exclude the hazard of early metastases. Thus, the prognosis may be grave in a patient with a short history and an active cancer, or the prognosis may be good in a patient with a long history and an inactive cancer. All things being equal, however, the longer a breast tumor is present, the greater the opportunity for growth, metastatic spread, and an unfavorable end result.

Many clinical investigators have correlated the time lag between the first sign or symptom of breast cancer and the onset of definitive treatment with

dissemination and prognosis. Since most tumors begin as a local proliferation and subsequently grow and spread, it has generally been accepted that the shorter the delay, the better the result. Regardless of our increasing diagnostic acumen, in this insidious and silent disease we are seriously handicapped by inadequate criteria with which to make a truly timely diagnosis. As aptly stated by Kreyberg, our surgical failures are the result of delay in the sense "that an important number of patients have already developed metastases, beyond therapeutic control, at the moment of the earliest possible diagnosis." All of us must become increasingly alert to the danger of breast cancer on less and less clinical evidence.

Significance of Tumor Size in Breast Cancer.—It is generally conceded that the size of the primary tumor at the time of diagnosis or operation is a very important factor in the prognosis of a patient with cancer of the breast. The smaller the size, the better the prognosis is considered virtually a self-evident truth. However, the validity of this assumption is not entirely without question.

Dahl-Iversen[7] noted that patients with small breast cancers are free of metastases or recurrences in 83 per cent of the cases three years after operation, whereas patients with larger tumors are free of recurrence in only 13 per cent after a similar postoperative period. Eggers, de Cholnoky, and Jessup reported a five-year "arrest" of 72.5 per cent if the primary breast tumor is 2 cm. or less, a 24 per cent five-year arrest if the tumor is between 2 and 6 cm. in size, and only a 15.5 per cent arrest for larger tumors. Haagensen and Stout noted a five-year clinical cure of 62.2 per cent if the breast tumor was less than 3 cm., and only a 19.8 per cent five-year clinical cure if the tumor size had reached 6 cm. or more. "The data indicate, as might be expected, that the prognosis becomes worse as the size of the tumor increases." In a later report, Haagensen[22] noted a mean diameter of 4.8 cm. in the clinical tumor size in a large series of patients with primary breast cancer. The incidence of axillary metastases in this group was 70 per cent. In contrast to this, a highly selected group of patients were studied in whom the clinical tumor size measured less than 1.5 cm. The incidence of axillary metastases in this group was only 11 per cent. Since prognosis and ultimate survival are closely related to the incidence of axillary metastases, their correlated dependence upon tumor size, grade of malignancy, and duration of disease is obvious.

Stewart has studied the surgical pathologic material at the Memorial Hospital in New York. Based upon tumor size recorded by the pathologist (Table XIII), Stewart believes that "in infiltrating mammary carcinoma, the most significant data for purposes of group prognosis, but not individual cases, are the largest diameter of the primary tumor and the condition of the axillary nodes."

Eggers, de Cholnoky, and Jessup found that the percentage of axillary metastases was in direct relation to the size of the tumor. There is progressive axillary involvement with increasing size of the tumor.

TABLE XIII. FIVE-YEAR CLINICAL CURE RATES IN CANCER OF THE FEMALE BREAST ACCORDING TO SIZE OF THE PRIMARY TUMOR (PATHOLOGIST'S DIMENSIONS, MEMORIAL HOSPITAL), BASED ON 1,355 PRIMARY OPERABLE CASES OF PATIENTS TREATED BY RADICAL MASTECTOMY WITH DETERMINATE END RESULTS (1935-1942 ADMISSIONS)

LARGEST DIMENSION OF PRIMARY TUMOR	CASES AND PERCENTAGE	BREAST ONLY INVOLVED	BREAST AND AXILLA
Less than 2 cm.—number of cases	201	121	80
5-year clinical cure rate, per cent	74.1	87.6	53.8
2.0 to 2.9 cm.—number of cases	396	185	211
5-year clinical cure rate, per cent	60.2	74.6	47.9
3.0 to 3.9 cm.—number of cases	318	119	199
5-year clinical cure rate, per cent	47.8	68.9	35.2
4.0 to 4.9 cm.—number of cases	183	65	118
5-year clinical cure rate, per cent	41.5	60.0	31.4
5.0 cm. and over—number of cases	257	57	200
5-year clinical cure rate, per cent	33.5	*75.4	21.5

After Stewart,[73] 1950.

*This figure may appear peculiar. It is somewhat elevated, because in the 5.0 cm. and over group there are included some of the bulky medullary carcinomas with lymphoid stroma which carry a better than average prognosis.

No further proof is needed to show the importance of early recognition of mammary cancer.

TABLE XIV. RELATION OF TUMOR SIZE TO AXILLARY METASTASES

TUMOR SIZE	0.5 CM.	1 CM.	2 CM.	3 CM.	4 CM.	5 CM.
No. cases	5	12	23	50	35	24
No. with axillary metastases	1	3	7	30	24	20
Per cent	20	25	30.4	60	68.5	83.3

After Eggers, de Cholnoky, and Jessup.[14]

Bloom, in a study of 350 cases, found the following five-year survivals:

Primary breast tumor less than 1 inch	59 per cent
Primary breast tumor 1 to 2 inches	45 per cent
Primary breast tumor 2 inches or more	32 per cent

However, as noted by Geschickter, "the size of the tumor is a reliable index of prognosis only if the pathological type is taken into consideration." Bloom, an advocate of the merits of histologic grading, believes that allowance must be made for tumor grade as well as size in determining prognosis. These three factors—grade, size, and prognosis—are considered in the figures in Table XV (after Bloom).

TABLE XV

GRADE	TUMOR SIZE (INCHES)	CASES	FIVE-YEAR SURVIVAL	
			NO.	PER CENT
I	1 or less	64	49	77
	More than 1	42	33	79
II	1 or less	68	40	59
	More than 1	81	27	33
III	1 or less	40	12	30
	More than 1	55	16	29

It is evident, from this study at least, that tumor size alone appears to be of no prognostic significance in breast cancer with either a high or low degree or grade of malignancy. In tumors which are Grade I, the prognosis is uni-

formly good regardless of size, and in tumors which are Grade III, the prognosis is poor regardless of size. However, only in Grade II does tumor size bear a direct relationship to prognosis—"the larger the tumor the greater the likelihood of spread having taken place."

On the other hand, Kunath stated that "an analysis of this point failed to reveal that a larger tumor carries any more serious prognosis than does a smaller one." Hoopes and McGraw also concluded that there was no correlation between postoperative survival and initial tumor size.

Considering the importance of determining the significance of tumor size in the prognosis of breast cancer, Kreyberg and Christiansen have critically analyzed 974 cases of breast cancer. The fate of their patients was carefully followed for from ten to twenty years. Only fifty-six tumors (5.7 per cent) were small (the size of a hazel nut or smaller), and of this group, 66 per cent of the patients survived five years or longer. If Grade I tumors were eliminated, only one-third of the patients then survived. Considering only the very smallest tumors in the "small" group (the size of a pea or bean), this study revealed a ten-year survival of 50 per cent. Kreyberg and Christiansen concluded that size alone is not decisive and that small tumors in clinical Stage I or Stage II do not indicate a more favorable prognosis than one might expect for similarly classified cases of breast cancer of larger size.

Thus, the prognosis based upon tumor size or duration of disease certainly cannot be regarded as an infallible index of survival. The matter must be more complex and dependent upon many factors such as degree of malignancy, growth rate, and host resistance. Although our tendency is to "celebrate our therapeutic triumphs when the degree of malignancy of a tumor is small," yet it is well to recognize the void in our knowledge regarding the still unpenetrated reasons for these more fortunate results.

Site.—The location of the primary tumor within the breast has been regarded by some with special interest in predicting prognosis. Lane-Claypon, in a detailed analysis of the frequency of site in 6,464 collected cases of breast cancer, found the upper and outer quadrant to be the anatomic area most commonly affected. This frequency is generally recognized in almost all series (Fitts and Donald[16] 58 per cent, Deaton, Postlethwait, and Bradshaw[10] 59 per cent), and various reasons have been given to account for this predilection of position. It has been pointed out that the axillary tail extending upward and outward may be especially exposed to various forms of injury incident to household chores or even brassiere straps and wire bands. The anatomic and functional relationship between the body of the breast and its axillary prolongation may be imperfect, resulting in secretory stasis and irritation. Nicholson and Grady[55] noted that breast cancer occurred in the upper half of the breast in 86 per cent of their series. Pre-existing benign breast disease caused by poor breast support was regarded as an important etiological factor predisposing to the upper half of the breast. Deaton and Bradshaw[9] suggested that breast cancer arising in aberrant breast tissue may

be difficult to diagnose, particularly when the aberrant tissue and normal tissue are contiguous. The most frequent location of aberrant breast tissue is in the upper and outer quadrant of the breast. It occurs in from 1 to 7 per cent of the normal population. Finally, it must be recognized that the major bulk of the breast tissue actually occurs in the upper and outer quadrant, thus rendering it proportionately more liable to malignancy.

In a survey of 1,000 cases of breast cancer, Geschickter found that approximately 60 per cent of the tumors occurred in the outer hemisphere, 18 per cent in the inner hemisphere, and 22 per cent in the central area. The most common site was the upper and outer quadrant, which gave rise to 44 per cent of the tumors.

The incidence of breast cancer according to site has been shown to have remained rather constant over a long period of time (Table XVI) despite changes in feminine fashion and women's domestic chores. According to Bloom, the frequency of site noted at the Middlesex Hospital in London differs in no way from similar studies of a yesteryear. The overwhelming predominance of upper and outer quadrant tumors (44 per cent) is a most striking feature of Haagensen and Stout's most recent survey.

TABLE XVI. INCIDENCE OF BREAST CARCINOMA ACCORDING TO SITE (MIDDLESEX HOSPITAL)

	PRESENT SERIES (1936 TO 1942), 385 CASES		CAMPICHE & LAZALUS-BARLOW,[5a] 1905 (1747 TO 1903), 1,010 CASES	BECKTON,[1a] 1909 (1904 TO 1909), 230 CASES	TRUSCOTT, 1947 (1926 TO 1935), 836 CASES
	CASES	%	(%)	(%)	(%)
Upper outer	177	46	45	46	46
Upper inner	75	19	17	20	20
Central	35	9	20	15	13
Lower outer	54	14	12	13	12
Lower inner	19	5	6	5	5
Axillary tail	7	2	-	1	4
Diffuse or whole breast	18	5	-	-	-
Total	385	100	100	100	100

After Bloom,[2] 1950.

The relationship between site of tumor and prognosis has been given serious consideration by many investigators. Some years ago Sampson Handley[28] pointed out that the prognosis of lesions located in the inner half of the breast was much worse than those located in the outer half of the breast. Handley attributed this to the greater risk of metastases to the mediastinum and lung along the crucial avenue of the internal mammary lymphatics.

Bartlett[1] has demonstrated in a rather striking manner the importance of tumor site on the end results of surgical treatment.

Richards believes that the location of the tumor deserves much more attention than it receives, and site should be given "serious consideration in deciding upon the procedure to be followed." Hawkins found the five-year

survival rate for breast cancer of the inner hemisphere to be 52.1 per cent, as compared to 64.6 per cent for the outer hemisphere. Breast cancer of the lower inner quadrant, in the experience of Haagensen and Stout, had the highest local recurrence rate and the lowest cure rate throughout several carefully reported series.

TABLE XVII

	WITHOUT AXILLARY NODES, 5-YR. SURVIVAL (%)	WITH AXILLARY NODES, 5-YR. SURVIVAL (%)
Outer hemisphere	77	29
Inner hemisphere	47	4

According to Nohrman, the prognosis is significantly better for lateral tumors only in clinical Stage I of the disease. No difference in prognosis with a difference in tumor site could be demonstrated in Stage II. The data of Smithers and associates, corrected for expectation of life and for stage distribution within each group, revealed a slightly lower survival rate for inner quadrant lesions, but the figures were not considered statistically significant.

Some authors regard the upper and outer quadrant of the breast, and others the lower and inner quadrant of the breast, as being the site of poorest prognosis. In one case the proximity to the axillary nodes and in the other the relation to the internal mammary nodes is held responsible. A similar inconsistent but justifiable opinion has been expressed for the nipple region or central area of the breast. In the anatomy of the lymphatic system, both Rouvière[62] and Sappey[64] have clearly demonstrated the importance of the subareolar plexus. Grant, Tabah, and Adair[19] have shown experimentally the constant and characteristic pattern of lymph flow in the breast which occurs in a centripetal direction toward the areola. Drainage of the parenchyma of the breast occurs centrally to the critical subareolar plexus before outflow to the regional nodes occurs.

Lane-Claypon, in her comprehensive survey, concluded "that infection of the axillary glands occurs most readily from growths situated centrally and outwardly; that while growths situated 'inwardly' do not cause early involvement of the glands of the axilla they may be more dangerous than growths in other sites, owing to the easy access to the thorax." In a later and more extensive analysis of results, Lane-Claypon could find no evidence that prognosis varied according to tumor site. Breast cancer cases classified separately by clinical stages again showed no indication that prognosis differed in the various quadrants of the breast. Similar conclusions have been expressed by Truscott[75] and Hartnett. Bloom considered it "possible that growths situated in the sternal quadrants and in the nipple area carry a slightly worse prognosis than do those in the outer regions." As noted by Handley and Thackray,[27] these are the patients who are most likely to have internal mammary node metastases.

By applying the principle of histologic grading to the problem of tumor site and prognosis, Bloom found (Table XVIII) that site was of some signifi-

cance only in Grade I breast carcinomas. He concluded that the tumor site in cancer of the breast exerted no striking effect on end results. Thus, prognosis appears to be perpetually dependent upon many subtle properties, which when taken together may exert a powerful influence on survival.

TABLE XVIII. SITE, GRADE, AND PROGNOSIS

	OUTER HEMISPHERE			INNER HEMISPHERE		
		5-YEAR SURVIVORS			5-YEAR SURVIVORS	
GRADE	CASES	NO.	%	CASES	NO.	%
I	76	65	86	29	21	72
II	100	47	47	37	15	41
III	67	18	27	28	8	29

After Bloom,[2] 1950.

Factors of Prognosis in Recurrent Breast Cancer.—In a unique study of two groups of patients, who were (1) first seen for recurrent breast cancer, and (2) first treated by radical mastectomy and who subsequently developed recurrent or metastatic disease, Shimkin, Lucia, Low-Beer, and Bell[67] investigated the problem of prognosis both before and after recurrence. Although the work of the Soviet investigators, Shabad and Golbert,[65] and the Americans, Pack,[57] Slaughter,[70] and others, suggests that multicentric primary breast cancer may occur not infrequently, it is fair to assume that late recurrences and metastases almost always represent dissemination from the primary focus.

The data of Shimkin's study concerning 261 recurrent cases of breast cancer were compared with and combined with data concerning 372 cases of patients with primary breast cancer who developed subsequent recurrences and metastases. It was demonstrated that the length of life in the latter cases is dependent upon (1) the stage of the disease at the initial operation (Fig. 2) and (2) the type of first metastasis or recurrence (Fig. 3) noted clinically (local, osseous, or general).

The five-year postoperative survival rate of patients who eventually died of breast cancer was 36 per cent for Stage I patients, 20 per cent for Stage II patients, and 9 per cent for Stage III patients.

There appeared to be no relationship between years of survival and age of the patient at the time of initial operation. This study did not reveal a significantly greater proportion of rapidly growing breast tumors among young women. The clinical stage of the disease appeared to be unrelated to the patient's age.

The time following operation at which point recurrences or metastases might become manifest was influenced by the stage of the disease at the time of operation. Survival following the clinical appearance of recurrences or metastases bears a very close relationship to the length of life from the initial operation to the onset of secondary disease. The length of life after recurrence was influenced to a minor degree by the stage of the initial disease but was influenced to a major degree by the type of recurrence or metastases.

Following local recurrence the survival period was longest (twenty-eight months), following osseous metastases (twenty-four months) and after generalized metastases the survival period was shortest (ten months).

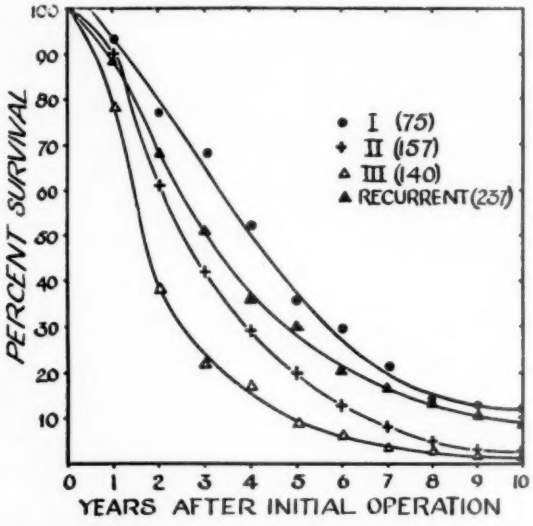

Fig. 2.—Survival of female patients with breast cancer treated by radical mastectomy. These patients subsequently developed metastases or recurrences and died of the disease. Graphically represented according to the stage of the disease at the initial operation, against years of survival after initial operation. Included is the survival of 237 patients who were first observed with recurrent or metastatic disease and who subsequently died of breast cancer. (From Shimkin et al., January, 1954.)

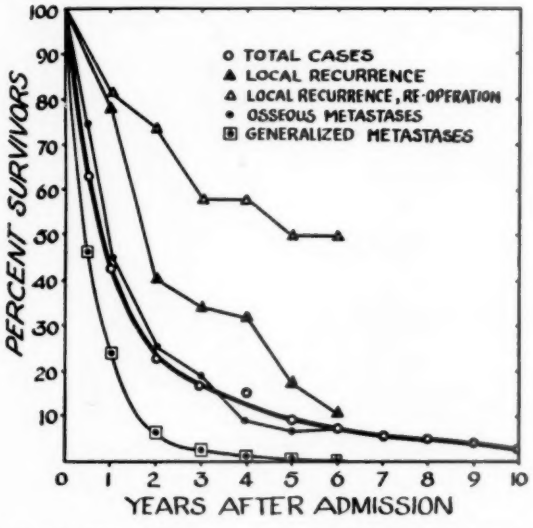

Fig. 3.—Survival of 261 patients with recurrent breast cancer, against years after admission to the University of California Hospital, by type of recurrence at the time of admission. Local recurrence fifty cases; osseous metastases thirty-one cases; and generalized metastases 143 cases. (From Shimkin et al., *Cancer*, January, 1954.)

SUMMARY AND CONCLUSIONS

The clinical problems of prognosis have been intensively studied by many investigators over a period of many years. A wealth of clinical and statistical information has been accumulated, but there still remains no unanimity of

opinion regarding its validity or significance as an index of prognosis for the individual patient with breast cancer. Each factor of prognosis is merely a straw in a wistful wind.

From scattered reports throughout the literature, Morton and Morton[53] have collected a series of unique cases indicating the inconstant natural history or clinical behavior of breast cancer. In some cases cancer may disappear spontaneously, while in others it may grow only in periodic cycles. Observed not infrequently is the phenomenon of delayed recurrence with local recrudescence within the area of operation many years after radical mastectomy. At times, tumor cells appear almost guileless by microscopic examination, lying latent and deceptively dormant within the natural defenses of the body. After a variable period of presumed quiescence, cancer cells often regain their flagging virulence and take on characteristics of rapid growth and extraordinary malignancy. Thus, prognosis is unpredictable, and cancer today gives no sure measure of cure tomorrow.

Tumors are known to vary greatly in their growth rate and in their tendency to metastasize early. The measure of earliness in time for the purpose of prognosis lies not alone in minutes or months but in malignancy and metastasis. The slender thread of time delayed, therefore, may mean that those patients who "lose a day lose a life." Prognosis is primarily a balance between the malignant potential of the tumor cell and the biologic resistance of the host. Radical mastectomy or even more extensive radical surgery promptly performed will be lifesaving only in those patients in whom the tumor has not yet spread beyond the confines of the field of operation. Thus, the prognostic significance and importance of axillary metastases (both presence and extent) or metastases to other accessible regional nodes are obvious. However, such factors as duration of disease, size, site or grade of tumor, and the age of the patient are in themselves uncertain prophets of prognosis.

Clinical attempts to determine the degree of cancer malignancy by evaluating the relevant factors of prognosis have been numerically expressed by Lee and Stubenbord[44] and Richards as the "Clinical Index of Malignancy." Such an assessment may be desirable to indicate tumor activity and, less likely, host resistance in a large group of patients, but the treatment policy in the individual patient can hardly be based upon an arbitrary numerical digit.

With true humility we must confess that despite prompt and adequate treatment, we do not know precisely which individual patient will be favored by fortune and granted a long survival. Certainly the cardinal concept of early diagnosis and early treatment well done cannot help but contribute toward this hope and expectation.

The most important measurable factor in the prognosis of breast cancer is the presence and the extent of axillary metastases at the time the patient is first treated. Age, duration of disease, size, site, and grade of tumor are all factors of secondary significance. Trauma, treatment, the effects of biopsy

and delayed operation, and pregnancy and lactation have not been considered in this discussion. The questionable influence of ovarian stromal hyperplasia on survival in both treated and untreated cases of breast cancer has been found by Sommers, Teloh, and Goldman[72] to be negligible.

While some of these factors may be related to the alertness and understanding of the patient and the diligence and initiative of the physician, as stated by Smithers and co-workers, prognosis "is largely dependent on the rate of growth and tendency to dissemination of the tumour."

In the dilemma of prognosis, currents and cross currents of biologic behavior flow beneath the surface of unpredictable clinical speculation. The measure of these forces and their influence on survival cannot as yet be calculated with exactitude.

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Appraisal of Progress in Surgical Therapy

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THE MANAGEMENT OF VENOUS THROMBOSIS IN THE LOWER EXTREMITIES

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INTRODUCTION

WHILE the incidence of venous thrombosis and pulmonary embolism shows considerable variation,[1] it becomes a more and more significant problem in the older age groups. Towbin[2] has recently pointed out that neither vital statistics nor clinical surveys or autopsy material give the true incidence of this form of terminal illness in the general population. At the Columbus State Hospital, pulmonary embolism was found in 25.7 per cent of 512 autopsies, with a marked increase in the older age groups.

Thromboembolism is much more than a postoperative complication and, as surgeons, we are often called to see it in traumatic cases, in medical patients, and in terminal illness. It is the purpose of this report to outline its management on our service and to take a stand in some controversial points which have agitated our profession for some time.

Depending on one's concept of the factors which bring about the clotting of blood within the vascular tree, therapeutic emphasis has been placed on combating venous stasis, on eliminating vasospasm as a concomitant factor, on decreasing the clotting activity of the blood, or on eliminating the localized clot from the general circulation by ligating or dividing the vein proximal to the thrombus.

While the incipient clot and its propagation are governed by many factors, our preference has always been to treat the lesion as a deficiency of the clotting mechanism and hence our emphasis on anticoagulants, notably heparin. While, in this appraisal of various methods of therapy, methods of diagnosis will not be discussed, it must be pointed out that (1) a number of "silent" clots escape our attention and become clinically manifest only when they propagate or cause embolism; (2) a group of patients exist in whom thrombosis may be suspected but never proved; and (3) various stages of acute thrombosis are discernible and their management must vary according to the stage in which they are seen. Elsewhere[3] these points were developed in detail.

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ANTICOAGULANT THERAPY

The surgeon's anticoagulant is heparin. There may be situations in which long-term anticoagulant therapy is necessary with coumarins. Early experience with Dicumarol, however, has taught us that its control by prothrombin levels is difficult, which really does not measure prothrombin alone but other clotting factors, and that the range between protective and hemorrhagic levels is uncertain and variable. Most important, the statistics which seemed to show significant decrease in the thromboembolic phenomena when Dicumarol was used after myocardial infarction are open to question.[4] For this reason we have completely abandoned the use of coumarins.

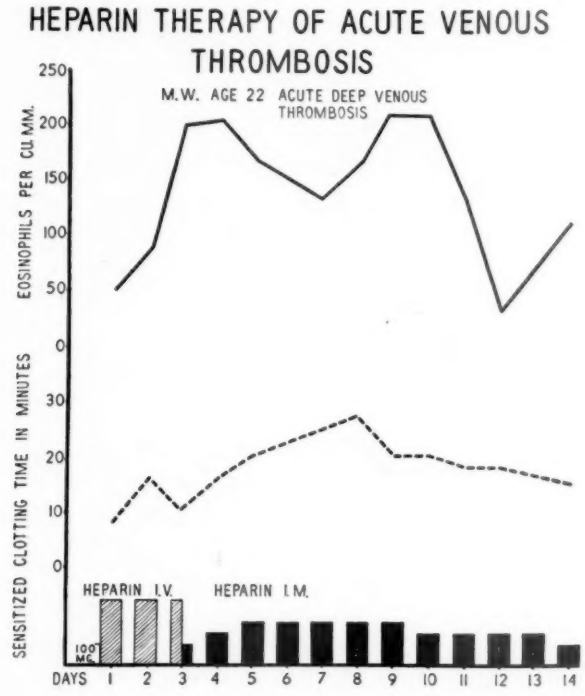

Fig. 1.—Heparin therapy of acute deep venous thrombosis. Treatment here was started with 300 mg. of heparin intravenously for three days followed by intramuscular heparin to the fourteenth day. Note that the eosinophil count rose and fell just like in any other form of acute stress. With the moderate doses of heparin the clotting time (the heparin-retarded clotting time mentioned in the text) has been kept between sixteen and twenty minutes, just slightly above the upper limit of normal.

A number of heparin substitutes have also been studied. They have side effects and are inadvisable for general use, although the latest one, dextran sulfate, is still under evaluation in our laboratory. Actually, heparin is the ideal anticoagulant, and only its price is objectionable. The fact that the oral or sublingual use is impossible makes it all the more efficient, since satisfactory and rapid concentration in the blood is desirable for its optimal action.

Methods of Administration.—A continuous drip, using 100 mg. of heparin to 500 c.c. of physiologic saline solution, 5 per cent dextrose, or blood, is used (a) intra-arterially through a polythene tube distal to a clamped artery when endarterectomy or vessel replacement is performed,[5] (b) intravenously through

a cut-down at the ankle when an acute iliofemoral venous thrombosis is treated by regional heparinization, and (c) in an arm vein in the presence of a rapidly spreading, malignant form of venous thrombosis with multiple emboli, usually encountered in diffuse, spreading carcinomatosis and being regarded as an exhaustion of the clotting mechanism characterized by great resistance to customary doses of heparin. The control of dosage by clotting times will be presently described.

The intermittent intravenous injection of 100 to 150 mg. of heparin in 1 per cent solution is given four to six times a day in the acute stage of venous thrombosis, thus an administration of from 600 to 900 mg. of heparin for a few days. This high dose should only be used in the acute form, to arrest and revert the process to a second stage when the patient's own resistance can come into play. When the fever, rapid pulse, and edema suddenly subside and when the daily eosinophil count rises, the dosage is sharply cut to 200 to 300 mg. of heparin in 10 per cent aqueous solution given in two to three *deep subcutaneous injections,* which are kept up by the nursing staff or in suitable cases by the patient himself, for a period of two to three weeks. While control with clotting times is obligatory during the large intravenous doses and for a few days after the subcutaneous doses are given, the clotting times may be omitted after they become stabilized, and then the patient may become ambulatory in or out of the hospital (Fig. 1).

We have abandoned the use of intramuscular heparin in a retarding medium[6] because it is painful and expensive and the plateau type of clotting time curves seems no more protective than the sharp peaks obtained with intermittent intravenous or subcutaneous injections in aqueous solution. One must fully agree with Bauer and his associates[7] that a high concentration of heparin is important in influencing the recent, loose clot, and hence we do not advocate subcutaneous heparin in the early acute phase of the disease.

THE LABORATORY CONTROL OF HEPARIN THERAPY

Heparin is far more than an anticoagulant, but its action in thromboembolic disease can be best measured by clotting times of the blood. In order for daily serial clotting times to be practicable on a general surgical service, one must postulate that the methods be simple and readily reproducible and possibly be run and reported at the bedside so as to direct the next dose of heparin. Two such methods have been used. *Capillary coagulation times* are simple, need no venipuncture, and, while very crude, give a good estimate of the patient's response to heparin, which notoriously varies not only in different patients but in the same patient in different stages of postoperative convalescence.[8] If no other method is available, this is a rapid bedside test; eight to twelve minutes of capillary coagulation time is a safe, desirable level. When intermittent administration is used these clotting times should be back to the preinjection level of three to four minutes before the next dose is given. During the first two days of therapy it is best to have at least two capillary coagulation times determined just before the next dose so that a stepladder type of curve can be avoided.

Far more preferable, however, is the use of venous blood; each 1 c.c. of blood is mixed with 1 μg of heparin in physiologic saline solution. Such tubes can be prepared in advance by the laboratory and kept in the icebox. Such a *heparin-retarded clotting time* has two great advantages over the commonly used single-tube or multiple-tube venous coagulation times: First of all, it neutralizes the varying amounts of tissue juice which is unavoidably aspirated by venipuncture and thus will give a slightly retarded clotting time. The normal range is between eleven and thirteen minutes, with a small scatter above and below this level.[9] Second, this clotting time is truly sensitized by heparin in that it will respond to anxiety, premedication, hemorrhage, shock, and surgical trauma with predictable fluctuations.[10] Such a postoperative clotting curve made up of daily determinations may even direct prophylactic administration of heparin (Fig. 2).

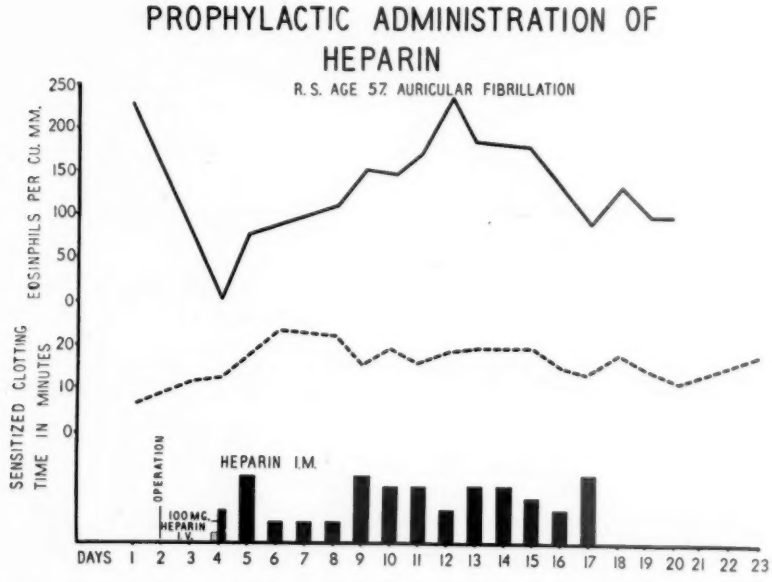

Fig. 2.—Prophylactic administration of heparin. The patient, R. S., underwent a hysterectomy and was treated with heparin starting the third postoperative day, because of a number of previous thromboembolic episodes including several femoral and cerebral emboli. Note again the fall, rise, and fall of the eosinophil count as a result of the operation and the even curve of the clotting time maintained slightly above the normal limit.

The desirable clotting time determined by this method is between sixteen and twenty minutes, and it may require massive doses of heparin up to 1,000 mg. during the acute phase to obtain it.[3] It has not been our aim to double or treble the normal level during anticoagulant therapy or prophylaxis but simply to restore the disturbed ratio of coagulant versus anticoagulant factors and push it slightly toward the anticoagulant side.

Heparin Sensitivity.—A small group of patients, whether they have had heparin before or not, show evidence of drug sensitivity such as flushing of the face, bronchospasm, nausea, and vomiting or diarrhea. An intravenous test dose of a few drops to 1 c.c. of heparin can detect these patients. Epinephrine is a good antidote should an alarming reaction develop after an initial, big dose.

The rate of injection should always be slow so as to avoid an unsuspected reaction. In a study of 256 patients receiving heparin, 8 per cent showed some degree of drug-sensitivity.[11]

Hemorrhage Due to Heparin.—Hemorrhage due to heparin may be encountered, being due to a cumulative effect, more heparin being given daily than degraded or excreted. Thus, on a prophylactic dose of 200 mg. of heparin, the clotting curve may slowly rise and thus gives sufficient warning to reduce the dose. Another cause of hemorrhage is the failure to cut the massive doses advocated in the early, acute phase of thrombosis, when the patient's sensitivity to heparin returns. But the most frequent cause of hemorrhage after heparin occurs in postoperative patients receiving heparin for prophylaxis. Here the patient's sensitivity to heparin normally rises around the third or fourth postoperative day, in the phase of defense; together with defervescence and rise of eosinophils, the patient's response to heparin is increased. Therefore, greatest care should be exerted during postoperative convalescence. In Fig. 2, a clotting curve is shown for a patient who has had multiple embolic phenomena from a fibrillating heart and who required a hysterectomy for endometrial carcinoma.

Should hemorrhage still occur in spite of all precautions, protamine sulfate is given intravenously, 1.5 mg. to each 1 mg. of heparin being entirely suppressive. For practical purposes, 100 mg. of protamine sulfate given intravenously every four hours until bleeding ceases is highly effective. It may fail, however, when a massive hemorrhage has brought about a hemorrhagic state independent of heparinemia and presumably due to a shocklike state in which fibrinolysis and low platelet count appear. Blood transfusions are, of course, our best standby, but they may again increase hemorrhage unless the blood is carefully crossmatched.

Although heparin is used extensively on our service, in 100 to 150 patients a year, only one massive hemorrhage was encountered in the last few years and this was due to overdosage combined with a paravertebral block. A huge retroperitoneal hematoma was later followed by cord symptoms.[12]

PROXIMAL VEIN LIGATION

I am convinced as ever that a deep vein should never be ligated or divided for prophylaxis or treatment of thromboembolic disease unless the patient cannot be given any heparin or unless, in spite of adequate anticoagulant management, thromboembolic phenomena continue. A deep vein is an important afferent channel, and even if it does frequently recanalize after an old thrombosis leading to incompetent valves, regurgitation of blood on standing is still preferable to obstruction of a main draining channel on exercise.[13]

Pulmonary embolism occurs in a large percentage of cases, roughly in one-half of them without preliminary warning and with no obvious lead as to its origin. To assume that 90 to 95 per cent of the thrombi originate from the veins of the lower extremities is an error. In a study of ninety-seven fatal pulmonary emboli verified by autopsy, Fowler and Bollinger[14] found that the heart was the site of origin in 52.8 per cent of all cases and, of the remaining 47.2 per cent of fatal pulmonary emboli originating from venous thrombosis, over one-half of

the thrombi were from the pelvis and possibly *one-third had originated in the lower extremities.* For this reason, we have always used the principle of proximal vein ligation most sparingly. This is not to say that ligation of deep veins in thromboembolic disease should never be done. *The common femoral vein* is ligated prophylactically prior to all major amputations because of the considerable incidence of pulmonary embolism in the arteriosclerotic group[15] and because the stump responds to anticoagulant therapy with hematoma and subsequent fibrosis. The *vena cava* is ligated in patients with iliofemoral thrombosis, especially if bilateral, when a pulmonary embolus has already occurred, or in the presence of multiple ones which anticoagulant therapy is unable to control. Subsequent emboli carry a higher mortality than the first, and here the operation is lifesaving.

Both of these operations leave residual edema and other sequelae of increased deep venous pressure, for which reason they are employed with strict indication. While blood dyscrasias contraindicate heparin therapy, renal and hepatic impairment simply call for decreased dosage and do not call for vein ligation. There is no indication for prophylactic or therapeutic division of *the superficial femoral vein* since it does not prevent embolism from the area served by the profunda or pelvic veins and may even increase its incidence.[16] It is true that performed for prophylaxis it produces no residual edema, but it also offers no protection and we cannot see any justification for its use.

TECHNIQUE OF LIGATING THE COMMON FEMORAL VEIN

The operation is performed under local anesthesia using 0.5 per cent procaine solution with 3 drops of epinephrine to each 1 ounce of procaine (Fig. 3). The longitudinal incision is made exactly over the pulsating femoral artery or, when this is absent, at the inner third of Poupart's ligament. The vertical incision is placed one-third above and two-thirds below Poupart's ligament. The subcutaneous fat and superficial tissue are incised vertically, and the long saphenous vein is gently retracted medially. The deep fascia is entered longitudinally about one-half inch laterally from the trunk of the saphenous vein at the saphenofemoral junction. Lymph glands should be displaced laterally. The arterial pulsation leads one to the vascular bundle; in its absence the medial border of the sartorius muscle is cleared and retracted. The neurovascular bundle contains the common femoral artery, the saphenous nerve, and the common femoral vein; at this level the artery is in front, the vein behind it with its medial border visible under the artery. The saphenous nerve should be carefully dissected out of the field and retracted. If it is firmly bound down to the artery and vein, it is best to resect it because a saphenous neuritis often follows not only iliofemoral thrombosis but ligation of the femoral vein. Separation of the artery from the vein is often difficult because of the organized exudate in the vascular sheath. Great care is exerted not to produce much traction on an inelastic rigid artery, since an atheroma may be loosened or an intramural hematoma may produce thrombosis. Narrow umbilical cord tapes are used to hold the artery laterally while a Mixter forceps threaded with No. 40 cotton is inserted around the vein. The site of double ligature or division between ligatures

should be well above the profunda and the saphenofemoral junction. In case of doubt, the vein should be opened so that clots can be aspirated from the proximal and distal segments.

Extraction of the clot by suction and resuture of the free vein has been suggested years ago and again revived recently by Mahorner.[17] The presence of distal clots in the leg is almost certain, and such a procedure should only be considered in case of intense regional heparinization. Since thrombectomy should not be practiced without heparinization, its usefulness is obviously very limited.

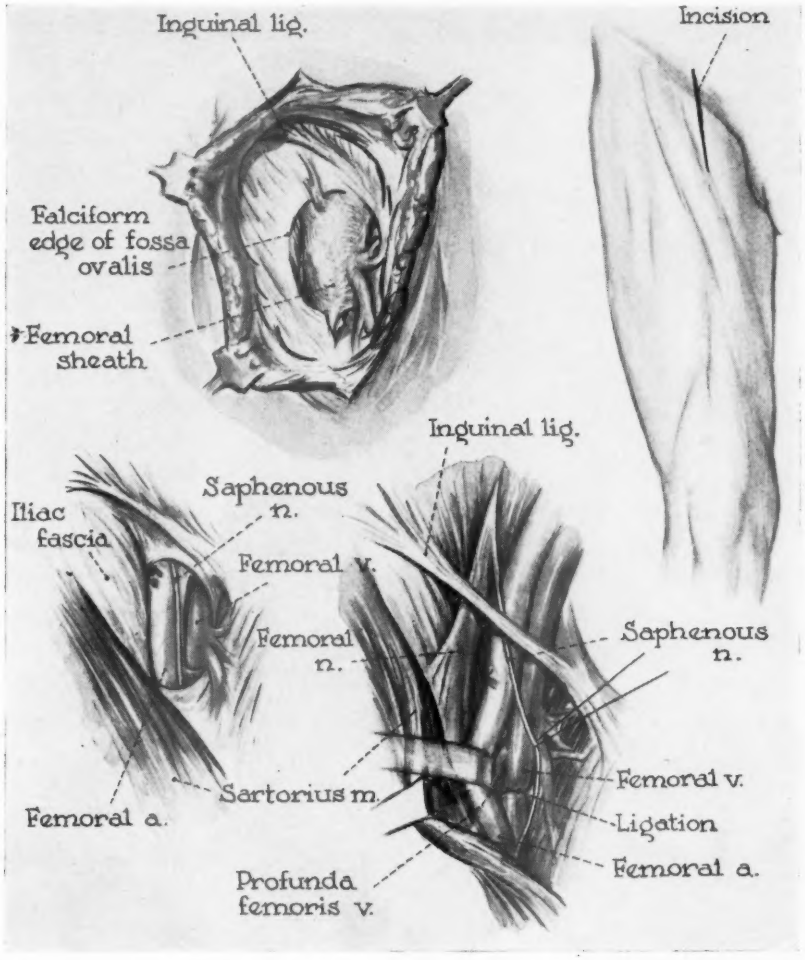

Fig. 3.—Technique of ligating the femoral vein. Note the longitudinal incision over Poupart's ligament, the exposure of the fossa ovalis, the exposure of the femoral vessels within the vascular sheath, the careful preservation of the saphenous nerve, and finally the ligature of the femoral vein, which here is shown to be below the profunda. In case of prophylactic ligation of the femoral vein prior to amputation, the ligature is placed above the profunda and above the saphenous vein.

The wound is carefully closed with No. 60 cotton, obliterating all dead space. During convalescence, the foot of the bed is elevated from six to eight inches and a snug elastic compression is maintained from toes to groin. The patient may

be out of bed and walking around in three to four days or earlier if the edema in the calf is slight or moderate. Amputation stumps are snugly dressed with elastic bandage and elevated on a pillow.

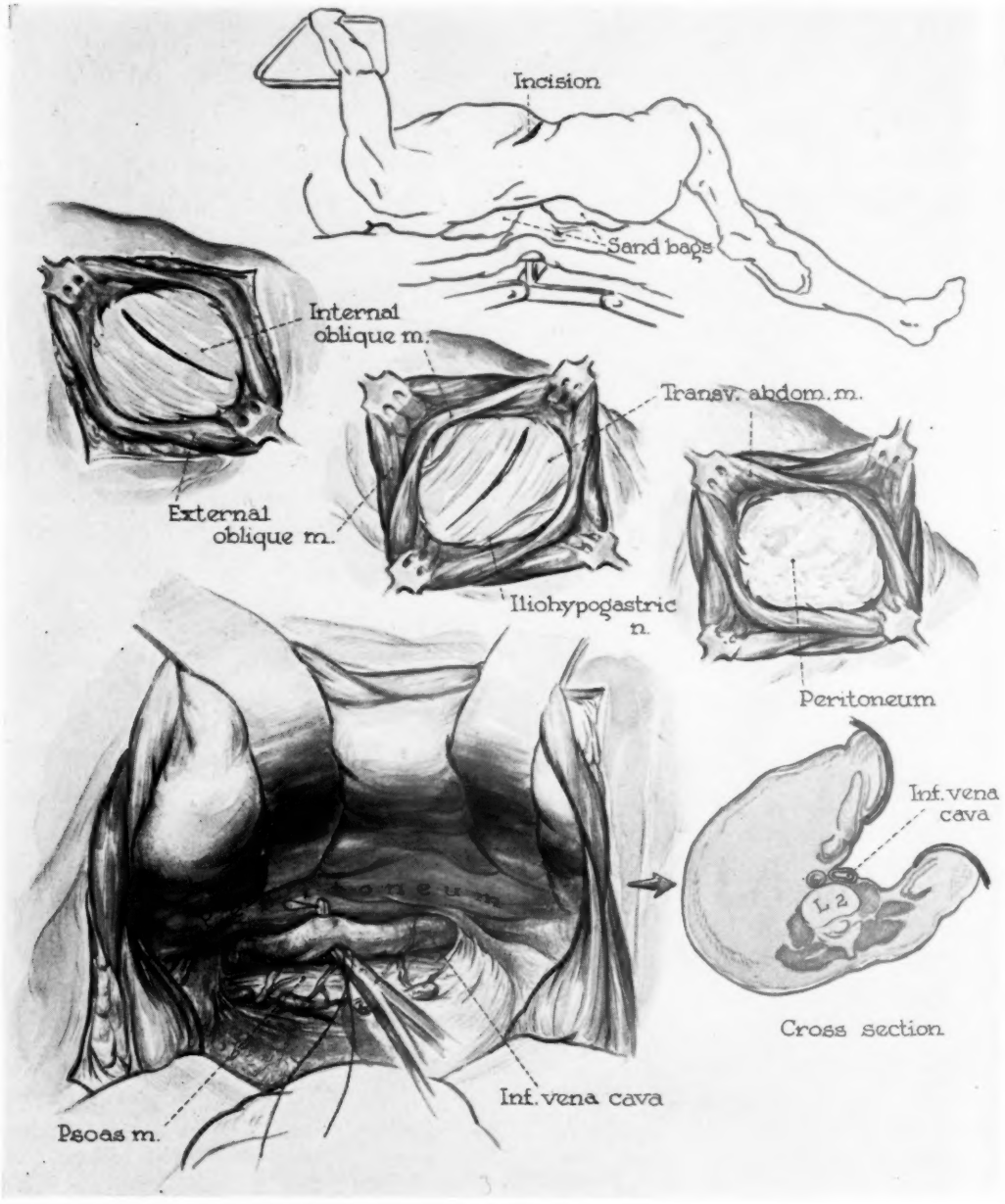

Fig. 4.—Extraperitoneal ligation of the vena cava. The approach is that used in a low lumbar sympathectomy, as described elsewhere.[18] Note the important position of the patient on the table, the splitting of the three abdominal muscles along the course of their fibers, the wide retroperitoneal mobilization, and the ligature of the inferior vena cava above the common iliac veins and certainly well below the renal veins. A No. 20 cotton ligature is carried by a threaded Mixter forceps. The wound is then reconstructed in layers without drainage.

LIGATION OF THE VENA CAVA

This operation has been performed only a dozen times on our service, both transperitoneally and extraperitoneally. Since many of the patients are acutely ill, just having suffered a recent pulmonary embolus, a right-sided anterolateral extraperitoneal approach, as described for lumbar sympathectomy, is preferred (Fig. 4).[18] Under a unilateral spinal anesthesia, with a little intravenous Pentothal to dull consciousness, the patient is placed on the operating table with the right flank elevated midway between the prone and lateral position, the table broken, the kidney rest elevated, and the right hip and knee acutely flexed so as to relax the psoas muscle. The incision starts at the costal margin in the midaxillary line and extends distally to the lateral edge of the rectus muscle along the course of the external oblique muscle. "The shorter the external incision the greater the internal struggle."[18] The external oblique, the internal oblique, and the transversalis muscle and fascia are split along the course of their fibers. The extraperitoneal fat is swept medially with gauze sponges, well past the midline. This maneuver exposes the vena cava, which may be surrounded by inflamed fat and lymph glands and adhere to the aorta. Carefully avoiding lumbar veins, a Mixter forceps, threaded with a No. 20 cotton strand, is gently passed around the vena cava. A second strand of cotton is applied around the vein. Both ligatures are *slowly* tied, while the patient's blood pressure is watched, since the sudden decrease in venous return may result in acute hypotension. A Trendelenburg position is advisable during and immediately after this procedure, and the wound is reconstructed in layers, no attempt being made to section the vein between the two ligatures. Snug six-inch-wide elastic bandages are placed over both lower extremities from toes to groin. The patient is kept in bed in a Trendelenburg position for four to five days and must sleep with the foot of the bed elevated with eight-inch blocks for many months. Well-fitting elastic hose, glycerin casts, or Gauzetex bandages are used to minimize the edema. The extent of this will depend mainly on the location and extent of venous occlusion prior to the ligation of the vena cava.

PARAVERTEBRAL SYMPATHETIC BLOCK

The technique of paravertebral blocks is so familiar today that I shall refrain from describing it. Its use in the treatment of acute venous occlusion has been limited on our service (1) to patients who exhibit marked vasoconstrictor activity in the affected limb, manifesting itself in a cold, damp cyanotic extremity with decreased or absent pulses and (2) to patients complaining of severe, deep, constricting visceral pain which can be abolished by the interruption of sympathetic fibers. In the majority of patients, the extremity is warm with the throbbing of inflammation, and the oscillometric curves are high.

In many hospitals today, the department of anesthesia performs these and other diagnostic and therapeutic nerve blocks. This might be desirable for the training of residents in anesthesia and because of the rare opportunity that the surgical residents have to study and practice such blocks. On a vascular surgical service the surgical resident's training should include these blocks be-

cause of the multiple diagnostic and therapeutic aids received from this procedure. Under no circumstances should these blocks be performed during effective anticoagulant therapy.

ENZYME THERAPY OF THROMBOSIS

Since spontaneous lysis of clots occurs both in vitro and in vivo, a number of investigators have been tempted to employ fibrinolytic agents to dissolve fresh, unorganized clots. These attempts are in the experimental stage, but our limited experience with intravenous trypsin has convinced us that in its present form this treatment is not advisable and is not without side effects. Most important, the patient is being deprived of the benefit of heparin while being subjected to this form of therapy. It may well be, however, that other stimulants of fibrinolysis will be found, since this is an important homeostatic mechanism.

DISCUSSION

Thromboembolic disease, according to a concept long held by our group, is caused by a failure of the clotting mechanism to cope with an incipient and most often subclinical, segmental thrombosis. For this reason, heparin has been the chosen therapeutic agent. It can be readily admitted, however, that poorly used heparin, just like Dicumarol, may do more damage than if the disease is permitted to subside without any outside help. The iatrogenic thromboembolic disease, originating from insufficient dosage of anticoagulants has been described elsewhere,[3] and attention should be called to large doses of heparin in the acute stage of thrombosis. Chronic recurrent thromboembolic disease is not under discussion here, but it often originates from (1) inadequate anticoagulant therapy, (2) prolonged bed rest and immobilization, and (3) unnecessary vein ligations creating areas of stasis resulting from ligature of patent main veins. Ligation or division of veins therefore should not be undertaken except as a lifesaving procedure or when propagation of thrombi from a readily localizable source cannot be undertaken with heparin.

SUMMARY

The treatment of choice in acute thromboembolic disease is by heparin. Vein ligation has a small, limited indication, and paravertebral block is useful to combat vasospasm and vascular pain when these are present. Enzyme therapy has not attained clinical stature at this writing.

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Book Reviews

Surgery of the Elbow. By Frederick M. Smith. Pp. 340. Springfield, 1954, Charles C Thomas, Publisher.

This is yet another of the excellent monographs on orthopedic subjects to be published by Thomas. It is concerned almost exclusively with the management of fractures and dislocations of the elbow. The material is well organized and very succinct. This book is not a review of the literature. It is not a reference book. It is a very straightforward practical exposition of the management of fractures and dislocations of this most difficult region. It is based upon the personal experience of the author. This is a volume that would be profitably read by any physician managing fractures of the elbow. Both author and publisher should be complimented for compressing so much useful information into such a small space.

Krankengymnastik in der Chirurgie. By W. Kohlrausch. Pp. 101, with 36 illustrations. Berlin, 1954, de Gruyter & Co.

The author of this monograph is not satisfied with the hit-or-miss exercise given the postsurgical patient under the heading of early ambulation. He feels that every surgeon, during the postoperative course of the patient, should employ a systematic program of gymnastics and exercises designed to fit every case. The first part of the book is a discussion of those exercises indicated for particular diseases and conditions. The second half of the monograph consists of a description of the various techniques to be used. For those who can read German, this is a valuable monograph because it stresses the importance of physical rehabilitation of the postsurgical patient and provides the information necessary for implementing such a program.

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